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By EDWARD MEAKIN LIVINGSTON, B.Sc., M.D.
Associate Visiting Surgeon, Bellevue Hospital, New York

THIS WORK in twenty chapters covers not only the clinical aspects of the abdominal cavity and peritoneum, but also the anatomy, physiology and surgery with special attention to visceral neurology, which has been sadly neglected to date.

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The Relation of The Intestinal Tract and Diet to the Treatment of Arthritis*

By Ralph Pemberton, M.S., M.D., F.A.C.P., *and* E. G. Peirce, A.B., M.D.,
Philadelphia, Pa.

Part One

The Relation of the Intestinal Tract

THE problem of arthritis is the subject of an increasing amount of attention from the laboratory as well as the clinical standpoint. Because of this, various analyses of the problem which have fallen upon somewhat barren soil are now beginning to receive the consideration they deserve. This is true of so fundamental an aspect of the problem as the classification of Nichols and Richardson,[1] first published in 1909, but only now becoming widely known; and of certain fundamental orthopedic considerations, regarding "postural exercise", having to do with the mechanism and function of the body as a whole. It is also true of the therapeutic importance of a low calorie diet in arthritis and of the etiologic importance of the gastrointestinal tract and the therapeutic consequences secondary thereto. This dietary phase of the question was developed by one of the present writers in 1912 and in a considerable number of subsequent publications, but has recently had additional emphasis at the hands of Fletcher.[2] This worker has adduced evidence from the x-ray standpoint relating to the intestinal tract which necessitates a further widening of our visual angle toward the disease.

That infection plays an important rôle in arthritis and many other conditions cannot be gainsaid. The present article constitutes in no sense an attempt to minimize its proven importance. The proper emphasis placed upon the infectious factors productive of arthritis and many other conditions has resulted, however, in undue domination of this concept and lack of inquiry as to how infection operates. In many instances the background upon which infectious processes become operative is laid long before these processes actually developed. Heredity, the constitutional makeup, the bodily configuration and other factors constitute prodromata which should excite active suspicion and should usually permit of prevent-

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Received for publication, Oct. 31, 1931.

The work here reported is part of a study on Chronic Arthritis in collaboration with Dr. Robert B. Osgood of Boston. The expenses of the investigation were defrayed by contributions from various sources, including a number of patients.

ing onset of the disease. Neglect of these considerations cannot be condoned in those who attempt to treat arthritics. It is increasingly clear that factors quite other than infection may operate to induce and perpetuate the disease. It is no longer sufficient to state that a certain organism was found in a tooth or prostate and to administer the respective vaccine. Therapeutics which begin and end here, already constitute, in the eyes of many students of the subject, evidence of unfamiliarity with it. There can be no question in retrospect that hosts of arthritics have suffered because of: first, extreme advocacy of the doctrine of focal infection; second, undue insistence upon, and even radicalism in, measures based on this concept; and third, because of the consequent exclusion of other measures, including even such generic agencies as those within the field of physical therapy. From a somewhat more philosophical standpoint, inquiry is now being made as to why infection arises in certain persons; why many such persons remain apparently well; why infection produces arthritis or other disease in some individuals; and how this result is brought about. It is not possible today to give a final answer to any of these questions. It *is* possible, however, to outline a number of factors which are definitely involved in these problems and to indicate certain therapeutic corollaries of importance attaching to them.

It is the purpose of the present article, therefore, to analyze further some of these factors; to adduce some corroboration of the work of others in relation to these factors; and to make more available to arthritics, through their medical advisers, certain forms of therapy which in consequence are seen to deserve greater emphasis. In this brief article only the developing aspects of the matter can be touched upon and the reader is referred to previous publications[3] for fuller details.

It has been pointed out by one of the present writers that reduction of diet is followed by definite benefit in a certain proportion of arthritics. Subsequent clinical experience has further incriminated the food intake and also the gastrointestinal tract in the production of arthritis. In a long series of cases the writers and their associates have been impressed by the frequency with which anatomical, topographical and physiological abnormalities of the intestinal tract can be demonstrated in arthritics by x-ray studies.[4] Others[5] have made the same observation.

In a recent series of x-ray studies Fletcher[2] has shown, however, that under appropriate conditions of diet, these abnormal configurations of the bowel, chiefly the large bowel, return toward or to normal. This is so much the case that subjects of arthritis, characterized by bizarre configurations of the colon, may no longer be recognizable from x-rays taken in the convalescent period. The implication is plain, that this abnormal condition is probably of etiologic and pathologic importance and that therapeutic effort which does not include consideration of this phase of the problem may be either incomplete or irrelevant. It is of course appreciated that the range of normality in the configurations of

the intestinal tract is wide. Some apparently normal persons possess abnormal appearing colons. This point is wisely emphasized by radiographers. It would be improper, however, to fail to give adequate consideration to the matter on this ground alone and the analogy can well be cited of the hosts of apparently well persons who harbor abscessed teeth. It should also be pointed out that the apparent emphasis placed here upon the large bowel, to the relative neglect of the small bowel, is referable to the fact that the former only can be visualized and studied in any detail by x-ray processes under present conditions of technique. In point of fact, the stomach shares in principle the deviations of the intestinal tract as a whole, as the gall bladder apparently may also. This statement is made to disclaim the intention of confining attention to the large bowel, as is the vogue in some circles.

In the attempt to explain the general situation above outlined Fletcher has advanced the view that the enlargement and tortuosity of the bowel encountered, are referable to an unbalanced ration and avitaminosis. In substantiation of this view he cites the observations of Rowlands,[6] and others[7] upon experimental animals in which these abnormalities have been produced by diets high in carbohydrate and low in protein and vitamins. An interesting phase of the question arises from the fact that these animals are prone to infection in the course of this syndrome. Indeed, Mellanby and Green,[8] have reached the conclusion that inadequacy of vitamin A is one of the essential factors in the development of low grade infections. Tisdall et al.[9] state that "a vitamin intake below the amount required for normal metabolism may produce conditions of ill health other than those commonly recognized as deficiency diseases." An important factor in the development of the general syndrome under discussion is the interesting observation that animals which acquire abnormalities of the bowel of the kind mentioned, fail to do so, even upon an avitamin diet, if given a ration low in carbohydrate but containing an adequate protein content.

Fletcher observes that these several factors have been precisely those which, partly by intent and partly incidentally, have characterized the type of diet long advocated by one of the present writers in suitable cases of arthritis. It is therefore wholly conceivable that the vitamins may play an important contributory rôle in the development of this syndrome. The problem is complicated, however, and it is not possible as yet to dogmatize as to the relative importance of the three factors mentioned.

With the aim of attempting further analysis of the question twelve cases of chronic arthritis were studied and are here cited, in which the bowel showed more or less return toward normal, as described by Fletcher, following successful treatment of the arthritic subject. They definitely confirm Fletcher's conclusions in this respect. Some of the x-rays illustrating the changes in the configurations of the bowel are not as striking as are many of those reported by Fletcher, partly perhaps because the cases were not treated with this end in view and

partly because of differences in the time intervals or other factors. Some are even more graphic. It is noteworthy, however, that when the x-rays of the first nine cases were presented at random without any data to the writers, it was possible, by observing the x-ray of the bowel alone, to select in each instance the picture taken during ill-health and that taken during or after convalescence. Typical x-rays are appended.

The lines of treatment in these cases differed and it becomes desirable to attempt some preliminary evaluation of the relative influence of the therapeutic factors operative. If, for example, some cases of arthritis illustrate the phenomenon of the return of an enlarged and tortuous bowel toward normal, following removal of focal infection alone or the use of physical therapy, somewhat broader relationships might be entertained. The following cases do not all permit, as yet, of final conclusions but the etiologic and therapeutic importance of this phase of the problem justifies presentation of the data at hand.

Case Reports

Case I. Mrs. R. C-n-l-y, aged 32, had atrophic arthritis of twelve years duration following typhoid fever. She had no demonstrable foci and presented a typical intestinal form of case. She made a practically complete recovery on dietary control together with betterment of her gastrointestinal function and a broad program of rest, physical therapy and tonic medication. The colon was long and dilated, with marked cecal stasis. This picture yielded radically to treatment and an x-ray taken during convalescence showed a graphic contrast.

Case II. Mrs. H--K, aged 55, hypertrophic arthritis, in menopause. She had no demonstrable foci but a long dilated colon with marked ptosis. This patient improved clinically on a balanced regimen of rest, diet, improvement of intestinal function, massage, heat and postural exercises. The x-rays taken during ill-health and convalescence showed a marked contrast. (See figures 1 and 2.)

Case III. Miss M. A-l-s-n, aged 65, hypertrophic arthritis. Typical intestinal case although she also had diseased tonsils. She made a complete recovery along purely dietetic lines in the presence of diseased tonsils. The gastrointestinal x-ray showed a long colon which improved markedly coincidentally with convalescence.

Case IV. Mr. W. A-st-g, aged 31, had severe atrophic arthritis of four years duration and wide spread involvement. The tonsils had been removed four years before. On admission he presented prostatitis and three abscessed teeth. The colon was long and dilated. The focal infections were removed or corrected, and a proper dietary was instituted, together with correction of his gastrointestinal function. A well balanced program of massage and tonic medication was established and the patient made a complete recovery. The contrasting x-ray pictures of the colon taken during ill-health and convalescence show marked differences.

Case V. Miss T. G-l-n, aged 48, had widespread atrophic arthritis. She showed a marked clinical improvement on a restricted diet. The intestine showed a very marked and relatively rapid improvement coincident with her clinical improvement. Fuller details in Part 2, case xiii. (See figures 3 and 4.)

Case VI. Mrs. Mc--m-r-a, aged 51, had hypertrophic arthritis of fifteen years duration. Her calf muscles were sore. Diseased tonsils were removed, a sinusitis was treated and several abscessed teeth were extracted. She showed a clinical improvement presumably following the above together with a regimen of regulated rest, modified diet, heat locally, general massage, and betterment of intestinal function. The bowel x-rays showed a distinct contrast.

Case VII. Miss J. E-a-s, aged 55, hypertrophic arthritis with Heberden's nodes. The onset abruptly followed a tonsillectomy and appendectomy two years previously. This patient made a complete recovery upon

dietetic lines coupled with improvement of the gastrointestinal function. The x-rays of the colon taken during ill-health and convalescence showed a definite contrast.

Case VIII. Mrs. S. H-n-y, aged 68, had hypertrophic arthritis with malum coxae senilis which caused her much pain. The muscles of her thigh were also very painful. Her diseased tonsils were treated locally. At the time of her admission her left thigh showed little rotation and flexion of her thigh caused the lumbar spine to descend. After a year of rest, diet, colonic irrigations, heat, massage and tonic medication the function of her left hip was much improved; her colon picture showed a corresponding improvement.

Case IX. Mrs. H. St--t, aged 48, had atrophic arthritis. This patient presented a long redundant sigmoid together with marked dental infection. The case improved after removal of the teeth and then "hung fire". Following correction of her diet and the marked intestinal stasis together with a full but well balanced program of physical therapy and tonic medication she made a complete recovery. The contrasting x-rays of the colon showed marked differences.

Case X. Mrs. G-st-l, aged 70, had hypertrophic arthritis. Her knees showed large overgrowth and some displacement of the tibial heads. She had diseased tonsils which were treated locally and two abscessed teeth which were removed. After this, the patient experienced a further improvement on a regulated life with periods of rest, local and general massage and a modified diet to which she was very faithful for a long time. At present, two years later, she remains in excellent condition. The x-rays of the bowel showed definite contrast.

Case XI. Miss E. A-h--d-ge, aged 53, had atrophic arthritis. This patient presented typical gastrointestinal invalidism

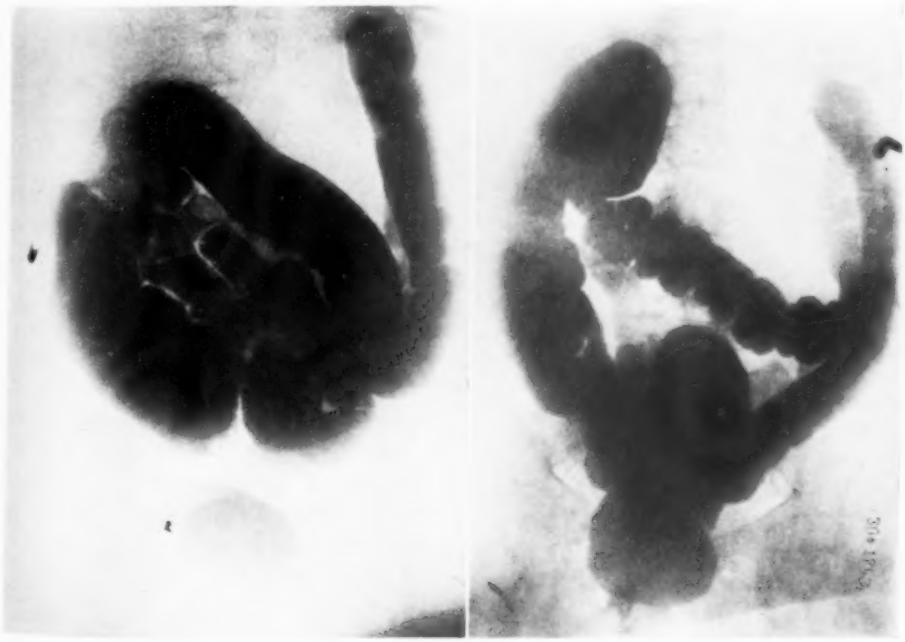

FIG. 1

Case II. Mrs. I. H--k.
A case of hypertrophic arthritis with the colon showing ptosis, lack of tone, reduplication, lack of haustra and regurgitation.

Case II. Mrs. I. H--k.
Appearance of the colon of the same patient following dietetic treatment. Note the improvement in tone, haustral markings and shape.

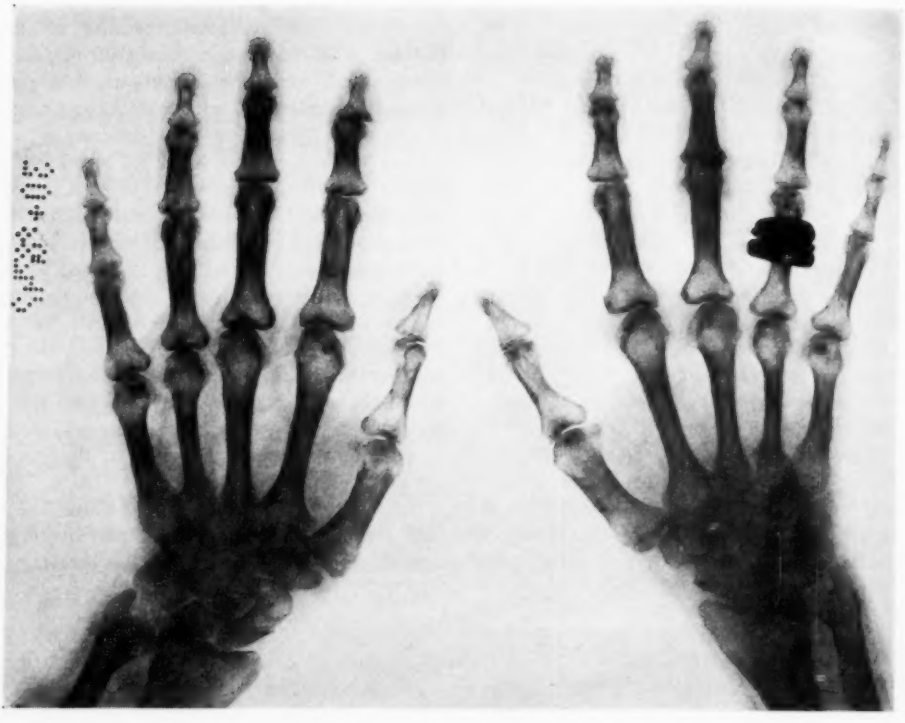

FIG. 2. Case II. Mrs. I. H--k. Hypertrophic arthritis.

and had lived for years on a carbohydrate diet avoiding "acids", meat, etc. The tonsils were buried and contained some pus but were not removed. She made a complete recovery along dietetic lines coupled with improvement of her gastrointestinal function. The x-ray picture of the colon showed a definite change after convalescence as compared with ill-health.

Case XII. Mrs. A. M. Gr--n, aged 57, had hypertrophic arthritis. This was purely a gastrointestinal type of case. The tonsils had been removed four years before without benefit. She made essentially a complete recovery along dietetic lines accompanied by correction of her intestinal function. The contrasting x-ray pictures of the colon taken during ill-health and convalescence show marked differences.

In few of the cases studied could any one single form of therapy be adhered to, to the exclusion of others. It is possible, however, to evaluate with some confidence, the treatments used in each case. It is thus clear that the return of the bowel to or toward normal accompanies not only cases in which dietetics provided the dominant or exclusive therapy: (cases III, V, and XI) but also cases in which the removal of focal infection (cases IV, VI and IX) and the exhibition of physiotherapy (cases II and X) played a conspicuous rôle.

It may be concluded from the data now at hand that the abnormal contour of the bowel encountered in arthritis is one consequence, probably a very frequent one, of arthritis in general, whatever its etiology. It thus follows, as elsewhere[10] stressed, that once

established, the abnormal contour and, presumably abnormal function, of the bowel become an additional contributory or causative factor in perpetuating the disease. Arthritis thus may be originated by an infection, the removal of which in no way influences secondary consequences of this general nature. Furthermore, it is probable on theoretical grounds, and has been indicated on clinical grounds[11] that the above configurations of the intestinal tract, constitute, *de novo*, an original, exciting factor in the production of the disease. They may apparently be congenital and suggestions of this are not lacking in young children, as revealed by x-ray studies. These configurations may also be acquired through pregnancy, faulty posture and the various factors that make for visceroptosis of which they often form a part. The relation of heredity and the consequent bodily makeup of the individual to this phase of the problem of arthritis becomes, therefore, of great significance and justifies the emphasis placed upon it by Osgood and his associates.[12] It may be remarked that in these cases the gall bladder may be large, it may fail to empty adequately during conduction of the x-ray dye study and apparently shares with the gastrointestinal tract as a whole a condition of atony. The bile from such organs is by no means necessarily

FIG. 3

Case V. Miss T. G-l-n.
Atrophic arthritis, with the colon showing a voluminous sigmoid, an elongated transverse portion, and lack of haustral markings.

Case V. Miss T. G-l-n.
Colon of the same case of atrophic arthritis following dietetic treatment. The ascending and transverse portions are narrowed and shortened, and haustral markings appear where smooth surfaces formerly showed.

FIG. 4. Case V. Miss T. G-l-n. Atrophic arthritis.

infected. By the same token, the stomach may be atonic and present hypochlorhydria.

It is to be noted that both types of arthritis illustrated the change in the x-ray pictures of the bowel taken during ill-health and convalescence.

The dispassionate view to be taken is that the etiology of arthritis at large involves a cycle in which various factors are coordinated and that no one can be justifiably stressed, etiologically or therapeutically, to the exclusion of the rest. The writers desire to emphasize that any concept of arthritis which fails to entertain consideration of these broad relationships constitutes a grave injustice toward arthritics as a group.

PART TWO

RECENT DEVELOPMENTS IN THE USE OF DIET

The above studies afforded an extension of experience in the use of dietetics and justify some review or recapitulation of this field of therapy in the treatment of chronic arthritis. Another justification for this is to be found in the increasing emphasis now placed upon the two main types of arthritis and the consequent desirability of determining whether diet, or indeed any measure of therapy, has application more particularly or solely to either of these types.

In view of what has been said in Part One regarding the configuration of the large bowel, it becomes obvious

that the food intake and the intestinal function, using that term in its widest sense, are reciprocally concerned. Emphasis has properly been placed by Osgood, by the present writers and by others, upon adequate evacuation, especially by means of colonic irrigation, of the lower intestinal tract. Unduly popular with the laity, this has had considerable exploitation at the hands of certain enthusiasts. A wholly "mechanical" view of the problem, however, is not justifiable and the question is apparently not one of purgation alone, or of "washing out" putrefactive material or bacteria from the colon. As has elsewhere been stated,[3] the institution of an appropriate dietary often affords a more fundamental approach to adjustment of the labors which the intestine is asked to perform. Much or most of that which is removed by irrigation is, precisely that which is taken in by mouth. Diet constitutes a difficult chapter, not to be entered upon lightly, but in some instances it constitutes also the *sine qua non* of successful therapy. This statement is not to be interpreted as justifying narrow emphasis upon this, or upon any other, aspect of treatment, because, as will be mentioned later, a coordinated and well-balanced attack is the great desideratum.

As already stated, experience with a recent series of cases has made it possible to determine definitely whether the beneficial influence of a diet is confined to either type, thus throwing some light upon the etiology of the two types. This question will be developed by first reciting the cases concerned.

ATROPHIC CASES

Case XIII. Th-r-a Ga-l-n, aged 48, had atrophic arthritis of fourteen years duration, involving all the joints of her limbs. Diseased remnants of tonsils had been removed on the ward eight months before the present admission. She was costive and had a very long, reduplicated colon with ileocecal regurgitation. The patient was rested for a week in bed in the ward, on *ward diet*, before treatment was instituted. The ward diet is such as is given in most hospitals and is fairly high in carbohydrates. Objectively the patient became definitely worse during this week and her hands and knees became more swollen and painful. After forty-eight hours on a relative fast, to be described, her hands became less swollen and more wrinkled. A further improvement in hands, knees and other joints followed the regimen below.

First and second day—juice one orange, t.i.d.; ample water.
Third day—juice one orange, 1 cup coffee, 1 dram sugar.
Fourth day—same as third, plus 8 ounces vegetable soup.
Fifth day—same as fourth day plus 3 Uneeda biscuits.
Sixth day—semi-liquid.
Seventh and eighth days—1221 caloric diet.
Ninth to thirty-eighth days—1465 calories.
Thirty-ninth day—1800 calories.

It will be noted that on bed rest plus a high carbohydrate and high caloric diet the patient became worse. On bed rest plus a low carbohydrate, low caloric diet she became promptly and definitely better. The improvement was beyond dispute and the patient volunteered similar evidence. (See Part One, case V.)

Case XIV. Mrs. M. B-ne-t developed atrophic arthritis following, or soon after, an automobile accident, six years prior to admission. She had typical lesions of atrophic arthritis in her hands. Injections of Coley's fluid had given her some help. The physical examination was negative except for a slight anemia. Infected tonsils and some abscessed teeth had been removed on a previous admission, without benefit. During the first week of the present admission the patient was put to bed and allowed to eat the ward diet. She became decidedly worse

as to swelling and pain in hands and knees, and was much discouraged. After three days on the orange juice regimen described under Ga-l-n (Part Two, case xiii) she showed improvement in her hands and felt better. The boggy swelling around the knuckles became much less noticeable and by the fifth day of the diet she could make a better fist. After five days on the orange juice diet she was given a day on semi-liquid diet; then for three days she was placed on 1403 calories and for the next six days on 1465 calories. She was discharged under observation very much improved as the result of diet alone, and has remained so eight months later. (See figure 5.)

Case XV. Miss El-n-r As-br-ge, aged 52, came in complaining of swelling and stiffness in her left hand and wrist which she had had for six months. She had been rheumatic all her life and had suffered much from stomach trouble, as a result of which she had been living, on medical advice, largely on various forms of carbohydrate, as being the most digestible foodstuffs. She was costive and depressed. The physical examination showed the heart slightly enlarged with a slight systolic murmur transmitted to the axilla. The arthritis was of the atrophic type. Her tonsils were infected and she had one questionable tooth. For various reasons these foci were not removed. Gastrointestinal x-rays showed duodenal

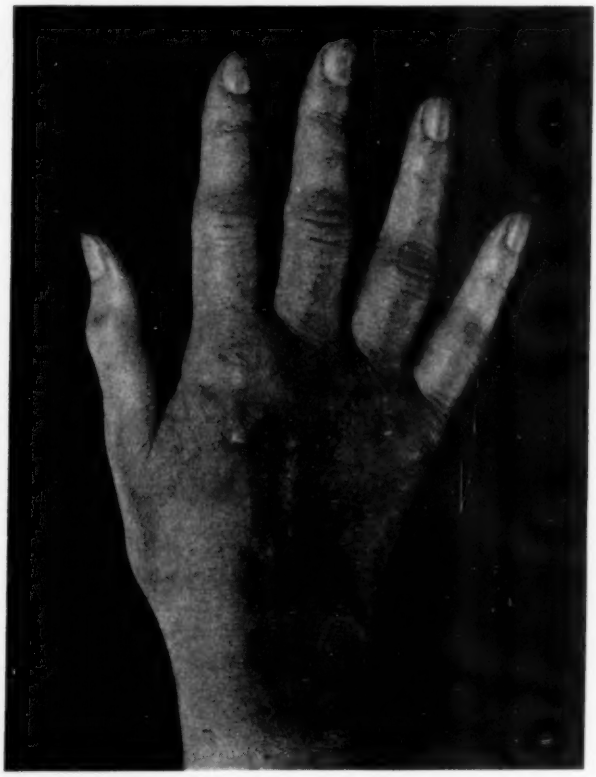

FIG. 5. Case XIV. Mrs. M. B-ne-t. A case of atrophic arthritis with improvement under dietetic treatment. The colon, by x-ray examination, showed marked changes coincidental with improvement.

stasis, a ptosed colon, the tip of the cecum fixed, bowel empty only after sixty-six hours. Atropine had helped her, but also made her costive. She presented the typical characteristics of the gastrointestinal invalid plus the syndrome of arthritis. Rest, colonic irrigation combined with colonic massage and a well balanced diet fairly low in carbohydrate and high in fat, with generous amounts of green vegetables and fresh fruits have been responsible for this patient's very striking recovery from her arthritic condition. Her disposition seems to have changed completely. She is now alert, cheerful and free from arthritis, adhering, though less rigidly, to the general principles of treatment.

Case XVI. Mrs. E. St-kd-le, aged 52, had atrophic arthritis of six years duration. This had followed diphtheria. The patient walked with a cane with great difficulty and pain, because of flexion of her right knee to an angle of 45°. She had also a tender right wrist and some pain in the left wrist, shoulders and elbows. She was found on examination to have a systolic murmur, a rapid pulse and a blood pressure of 188/110. She had bilateral sinusitis, posterior ethmoiditis and remnants of tonsils had been left from tonsillectomy. She was treated locally and conservatively for her sinus condition without operation. This patient was very tired and depressed during the first part of her hospital stay. She exhibited improvement first following a day on a low calorie orange juice diet. Her knee gradually extended under a treatment that consisted of a diet of 1465 calories, part time bed rest, heat and cautious massage to the knee daily. The diet of 1465 calories which was used for two months was as follows:

	Calories Protein	Calories Fat	Calories Carbohydrates	Calories Total
1. 1 egg, boiled	27.1	55.8	....	85
1 glass milk (hot)	29.8	81.8	41.6	157
30 grams bread	11.3	3.6	65.3	80
15 grams butter	.6	118.6	....	119
250 grams orange	6.2	2.3	87.1	96
Total	75.	262.1	194.	535
2. Lettuce q.s.				
8 oz. vegetable soup (strained)				
60 grams string beans	2.	6.1	4.7	13
Mayonnaise, 1 tbsp.	7.6	161.5	1.3	170
150 grams apple	1.8	4.2	66.4	72
1 glass milk	29.8	81.8	41.6	157
Total	41.2	253.6	114.	412
3. 100 grams chicken	131.6	40.9	8.6	181
50 grams spinach	4.3	19.	6.7	28
50 grams beets	3.3	.5	10.7	14
30 grams bread	11.3	3.6	65.3	80
15 grams butter	.6	118.6	....	119
250 grams orange	6.2	2.3	87.1	96
Total	157.3	184.9	178.4	518
Summary:				
	75	262	194	535
	41	254	114	412
	157	185	178	518
Total	273	701	486	1465

When the patient left the hospital she could walk with ease using a brace to protect the right knee from strain. She continued on the diet in modified form and later discarded the brace. She became entirely free from arthritis after following for many months the general principles laid down.

Hypertrophic Cases

Case XVII. Miss Mary A., aged 65, came in complaining of stiffness, aching and soreness in limbs and back, especially the knees, of five years duration. She had hypertrophic arthritis (figure 6). She gave a history of having severe eczema over a long period of time for which she had been treated by x-ray. The patient had formerly suffered from headaches. Her menopause had been attended by unpleasant manifestations. When first seen she had vertigo and was usually costive.

The physical examination showed a slight woman, reasonably well nourished, whose hands and knees gave evidence of hypertrophic arthritis. In all respects except those to be mentioned, her examination was not noteworthy; the cardiac dullness was slightly increased to the left; a systolic murmur was heard at the aortic cartilage and at the xyphoid, loudest at apex, with a leathery first sound; she had scattered râles in her chest; her liver border was palpable; in the upright position her abdomen was full and prominent. Her legs were both "bowed", especially the right, because of external slipping of the tibial head and her feet were flat with some pronation. Gall bladder x-ray dye studies showed a nonfunctioning gall bladder. Gastrointestinal x-ray studies showed a tortuous colon, sigmoid dilatation and ileocecal regurgitation. She had definitely diseased tonsils which, because of her age and cardiac condition, were not removed. A study of her dietary intake revealed that she ate an average of 1709 calories. She was given bed rest with general massage three times a week together with heat and massage as needed locally. She was put on 1540 calories consisting of a generous green vegetable ration, fresh fruit, butter, cream, meat and eggs, with relatively little carbohydrate. After thirteen days this was increased to 1700 which differed from the diet the patient had chosen for herself in being lower in carbohydrate and higher in fat. After eight days on 1700 calories the patient was allowed 1958 calories which included 1 dram of Ol. morrhuae, t.i.d. Five days later the diet was again reduced to 1540 calories. After two months in the hospital she left on 1700 calories. During her stay she made a decided improvement in her comfort in walking. She continued on her regimen outside with steady advance in the use of her limbs and is now well, two years later. *This patient never had colonic irrigations.* A picture of her colon taken after her convalescence shows that the colon has become less distended, shortened in certain parts, and that it shows the normal haustral markings more plainly.

Case XVIII. Mrs. Ada G-l-t, aged 54, had hypertrophic arthritis. She was a slight, nervous woman without much reserve strength. She came in complaining of stiffness and pain in her hands, knees and back. She had suffered from arthritis for nine years. She complained of tingling of her fingers and shins. She had cramps in her arms when carrying things. Her tonsils were out. She had no demonstrable focus of infection. Her blood pressure was 130/85. Her physical examination revealed that she had a slight systolic murmur, but no cardiac enlargement. Her right kidney, or liver, or both, were palpable. She had some tenderness over the gall bladder region. Her left foot was somewhat pronated. She rocked her hips in walking though both femora flexed and rotated well. Her hands showed hypertrophic changes. X-ray of the gastrointestinal tract and colon picture by enema showed the colon to be of a contracted type. She showed no advance on a regimen of rest, massage, bakes and colonic irrigations. She gradually improved, however, on a low caloric diet, inaugurated by a four day period of orange juice, oz. xii, q.d. After four weeks on a restricted house diet this was repeated with the addition on the second day of 1 dram of sugar, and four fluid drams of whiskey to each portion of orange juice. This was followed by a diet of 1062 calories of such a character that it would be absorbed high in the intestine. This diet continued for two days, after which two Uneeda

biscuits were added for two days. The house diet was then allowed for two days after which she was given for ten days a diet of 1500 calories, which was then raised to 1800 calories. The definite improvement in arthritic symptoms which the patient experienced at the end of her hospital stay was even more marked later after she had spent some time in a high dry altitude. She became able to lead an active life, riding horseback and entering into various pursuits, whereas when first seen she was a limping invalid. She was last seen "doing" a European art gallery on foot.

Case XIX. Mrs. B-r-ch, aged 52, had clear-cut hypertrophic arthritis. There were no focal infections. Her hands were involved to such an extent that she was unable to make a good fist. After being placed on the restricted diet described below, the patient became able in 6 days to flex her fingers markedly better.

First day—juice of one orange three times a day.
Second day—as above plus 1 cup of clear coffee and 1 teaspoonful sugar.
Third day—as above plus 8 oz. of strained vegetable soup.
Fourth day—as above.
Fifth day—as above plus 3 Uneeda biscuits.
Sixth day—semi-liquid diet.
Seventh day—1000 calories.
Eighth to thirty-eighth day—1200 calories.
After that—1465 calories.

The patient showed further improvement subsequently and was quite well nine months later.

Observations made on certain of the cases studied have amplified other observations made in the army, previously reported,[14] having to do with the application of dietetics in a radical manner involving underfeeding or starvation.

FIG. 6. Case XVII. Miss Mary A. Hypertrophic arthritis.

It was observed in the army that under conditions approaching starvation a surprising degree of restoration of function sometimes took place in joints which had apparently been largely or wholly ankylosed. This ankylosis was obviously of fibrous nature but there apparently takes place at times under these circumstances a relatively rapid improvement of local physiological processes, including possibly absorption of detritus, which results in a betterment of function that may be of the first importance to the arthritic subject. Thus, in advanced cases of the Strümpell-Marie type of atrophic arthritis, the spondylitis ossificans ligamentosa of Knaggs, there is usually definite limitation of movement in hips, knees, wrists, etc. Within the bony limitations of such residual movement, however, thickening, contracture and adhesion of the joint structures may further lead to complete or nearly complete immobility. It would appear from the as yet limited number of observations available, that sharp curtailment of diet, approaching starvation, may bring about restoration of movement within the range of true joint movement remaining, to a degree which has not been regarded as possible. Some analogy to this is seen in animals suffering from experimental rachitis in which a short period of starvation inaugurates processes of regeneration in the bone notwithstanding the inevitably unfavorable prognosis as to life if the starvation be maintained.[15] It is therefore valuable to cite the following two cases illustrative of this general state of affairs in arthritis.

Case XX. M-rg-t C-m-r, aged 24, had had atrophic arthritis for two years with pain and swelling in knees, ankles, hands and wrists. There was limitation of motion amounting nearly to ankylosis. All detectable foci were eliminated. She was in the hospital for two periods, the first for three months, during which time she made a limited improvement on physiotherapeutic treatment. On the next admission nearly a year later, she was put to bed and given a low caloric diet. During the regimen she was given no treatment other than rest and a low intake of food. The program was as follows:

First and second days—juice of one orange, t.i.d.; ample water.
Third to eighth days inclusive—as above, plus 1 cup coffee, plus 2 drams of sugar.
Ninth to eleventh day, inclusive—1078 calories.
Twelfth to fifteenth day inclusive—1196 calories.
Sixteenth to twenty-first day inclusive—1278 calories.
Twenty-second to forty-fifth day inclusive—1480 calories.

Six days after inauguration of the diet the patient had a larger range of motion in her wrists, upon measurement, and less tenderness in a swollen finger as observed by three persons. Subsequently the patient did well when able to adhere to the principles of treatment though the circumstances of her life made this difficult and sometimes impossible. She has recently married.

Case XXI. C-l-a D-v-k-n, aged 27, had atrophic arthritis of thirteen years duration. Practically all joints were involved and the left hip was ankylosed; the right hip was becoming stiff and painful. The condition had been very stubborn and the patient experienced no improvement on Small's soluble antigen, on bakes, on massage or on colonic irrigation. She was given a sharp restriction of diet as follows:

First day—juice of one orange, t. i d., ample water.
Second day—juice of two oranges, 2 drams sugar, t.i.d.,
Third day—juice of one orange, t.i.d.; one cup of coffee; 2 drams of sugar, 8 ounces strained vegetable soup.

Fourth day—as above, plus two Uneeda crackers.
Fifth day—liquid ward diet.
Sixth day to eighth day—house diet.
Ninth day to twelfth day—1065 calories.
Thirteenth to fourteenth day—house diet.
Fifteenth to twenty-fifth day—1403 calories.

By the fourth day there had occurred an increased range of motion in the right hip which had previously yielded to no other form of treatment. This betterment was maintained during the period of her stay in the hospital and subsequently. (See also case 26 in reference 14.)

The recital of these last two cases is perhaps rather of academic than of therapeutic interest because the proportion of cases with fibrous ankylosis which would so respond is doubtless small and such cases must be carefully selected. Furthermore, the improper use of such measures might work great harm in some subjects of unstable equilibrium, especially in the presence of hidden infections, masked tuberculosis, etc.

A recital of the above series of nine cases shows clearly the undoubted influence of a restricted diet in the treatment of *properly selected* cases of arthritis. A number of cases are detailed in which no complicating form of therapy was brought to bear. The two main types of arthritis, atrophic and hypertrophic, each showed great improvement or full recovery as a result of the same measures. This implies some commonality of etiology and pathology and will be made the basis of another communication. A chief point at issue here is that to withhold the possible benefits of diet from either type, on the basis of *a priori* convictions relating to different treatment of the two types is often to manifest an injustice toward the arthritic sufferer. *It is not recommended that cases of arthritis, en masse, be treated in this way because, as the writers have repeatedly emphasized, the successful therapy of arthritis consists in a properly coordinated use of the various measures available in this disease.*

It is particularly to be stressed that the measures approaching starvation detailed in these cases be not applied to arthritics in any wholesale way. The reader is specifically cautioned on this point. Underfeeding for any purpose is a two-edged tool which must be circumspectly used. The propriety of instituting dietetic treatment in arthritis must be determined *independently* in all cases. The factors concerned here have been discussed elsewhere at length, and the reader who contemplates applying these measures is urged to consult the references[16] cited for the necessary details.

Bearing in mind the precautions emphasized, it is to be pointed out that the use of diet constitutes in many cases a foundation for other lines of therapy which alone would be futile. The state of affairs favorably influenced by a low dietary is probably present in many or most arthritics but the extent to which the influence of this measure can be brought to bear is strictly conditioned by the nature of the causes of the arthritis, the extent to which these causes can be removed, the nutrition of the patient, the existence of complications, the degree and chronicity of invalidism, the extent of the activities of the subject, and many other factors.

Finally, brief preliminary mention can be made of the fact that in a

series of four cases of arthritis representing both the atrophic and hypertrophic variety it has been possible to bring about sharp subsidence of the disease on the basis of a low caloric and low carbohydrate intake in which all vitamins were definitely excluded. Improvement was none the less rapid or marked, however, and the implication is plain that the presence of vitamins does not constitute the essential factor in the production of the benefit achieved. This observation does not exclude the possibility that the vitamin content of the diet importantly influences the development of and recovery from the syndrome discussed. The analogy of reparatory processes under conditions of starvation in rachitis induced in experimental animals by avitamin diets may have application here. At present, however, the indications are that the low caloric diet *per se* constitutes the essential factor in the experiments mentioned and that the rôle of the vitamins becomes influential in a somewhat more indirect manner and especially over long periods of time.

Summary

Attention has previously been drawn to the frequency with which the syndrome of chronic arthritis, both atrophic and hypertrophic, is accompanied by enlargement and tortuosity of the large bowel. Corroboration is afforded, in the present contribution, of the work of Fletcher who has shown that, with institution of the type of diet previously described by one of the present writers, the bowel so distorted may return to or toward a normal contour. Apparently the condition described may sometimes be congenital or it may be acquired. Once established in the course of cases of different primary etiology, the condition described may constitute an additional contributory factor in prepetuating the disease. Arthritis may thus be originated by an infection, the removal of which in no way influences secondary consequences of this nature. It is equally probable that the above configuration and ensuing dysfunction of the intestinal tract also constitute an originally exciting factor in the production of the disease.

Dietetic therapy affords the *sine qua non* of successful treatment in a large number of cases of arthritis. *Such therapy should be applied, however, to appropriate cases only, and on the basis of a familiarity with the principles concerned and with the limiting factors to which references are given in the text.*

In amplification of earlier work, it is shown that under conditions of undernutrition approaching starvation, not only may the active symptoms of the disease subside but there may be also, occasionally, an absorption of detritus or pathological exudate in or around joints, nearly or quite ankylosed, which reduces the amount of limitation to motion imposed by the existing fibrous contractures. In *suitably selected cases* the gain so achieved, though necessarily of small extent because of bony impingements and the like, may have great significance for the activities of the patient.

Finally, preliminary report is made of the fact that cases of both types of arthritis have experienced sharp im-

provement upon low calorie diets from which all vitamins were definitely excluded. While in no way negativing the rôle of the vitamins in relation to the rheumatoid syndrome as a whole, in the sense above discussed, it is clear that the reduced food intake and not the presence of vitamins primarily determined the immediate and sharp benefit observed.

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Toxic Granulocytopenia, Purpura Hemorrhagica and Aplastic Anemia Following the Arsphenamines*†

By Adolph B. Loveman, A.B., M.D., *Ann Arbor, Michigan*

Senator[77] in 1888 reported four fatal cases of acute infectious pharyngitis. Unfortunately no bacteriological or hematological studies were made. Fourteen years later Brown[70] reported the first case of acute infectious pharyngitis with complete blood studies. The patient showed a marked leukopenia and on one occasion the polymorphonuclears were reduced to one per cent. From then until Schultz[75] reported his cases of agranulocytic angina, examples of an agranulocytic blood picture were described by Schwartz,[73] Türk,[72] and Marchand.[74]

As early as 1920, Moore and Foley[7] reported agranulocytic blood pictures following the arsphenamines. Since then many cases have been added to the literature.

A voluminous literature is now available on agranulocytic angina, most of which has appeared within the past few years. One of the most complete and enlightening is that of Baldridge and Needles.[55] They are entirely justified in their condemnation of the term 'agranulocytic angina.' They have shown very clearly and accurately that a-granulocytosis means, either an absence of a certain type of non-granular adult cell of myeloid origin (abnormal neutrophil), or else the term is derived from a-granulocyte-osis, in which case it would mean an absence of increase of granulocytes, that is a normal count. In modern medical nomenclature neither of the above interpretations is accepted. Since agranulocytic angina in the modern sense can exist without a true angina of the throat, this is added indication that Schultz's agranulocytic angina is an inadequate terminology. No doubt that which Schultz had in mind was a diminution to absence of granulocytes associated with a necrotic process in the throat, of unknown etiology, which terminated fatally. Since various factors can produce the above syndrome, which is preferably called granulocytopenia (Harkins[54]), it is felt that wherever possible adjectives should indicate etiology, such as toxic or septic granulocytopenia. For the cases described by Schultz, any of a number of names are more adequate; namely, idiopathic granulocytopenia, idiopathic granulopenia, or if it is desired to emphasize the necrotic process in the throat, idiopathic granulocytopenic angina. At

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the present time evidence is against idiopathic granulocytopenic angina being a clinical entity and favors its being a syndrome caused by various etiological factors. Time alone will tell whether there is some hitherto unknown cause responsible for the condition described by Schultz.

Evans,[58] at Johns Hopkins, first reported a case of hemorrhage following arsphenamine, in 1916. At the time, however, he regarded this as a mere incidental finding. It remained for three French workers, Leredde,[43] Labbé and Langlois,[33] three years later, to bring this before the eyes of the medical profession.

Farley,[9] in 1930, in reviewing the literature of all cases of bone marrow depression following the arsphenamines reviewed 39 cases and added 7, making a total of 46 cases. If, in our study cases have been uncovered which Farley failed to report, it is no fault of his, for such complications have been hidden under various titles and the articles have appeared in many languages, as well as in rather obscure magazines. It is entirely possible that certain cases have been unintentionally omitted from this report, but to our knowledge all cases available have been included. Many of the cases were unsuited for complete studies, but were used wherever possible in compiling our statistics.

A total of 64 cases of post-arsphenamine blood dyscrasias were found in the literature, with 31 deaths, a mortality of 48 per cent. Neoarsphenamine was the drug employed in 35 cases with 17 deaths; old arsphenamine was used in 10 cases with 5 deaths; sulpharsphenamine in 6 cases with 3 deaths; silver arsphenamine in 2 cases with one death; mixed arsphenamine therapy in 8 cases with 4 deaths. In addition, other arsphenamine preparations were used, the specific types of which were not stated, and in this group there were 3 cases with one death.

In the cases reviewed it was found that arsphenamine preparations attacked each element of the bone marrow, producing 30 cases of aplastic anemia with 18 deaths; 14 cases of purpura hemorrhagica with 5 deaths; and 15 cases of granulocytopenia with 6 deaths.

Under aplastic anemias have been grouped those cases in which there was a depression of all the elements composing the bone marrow; namely red blood cells, platelets, and polymorphonuclear leukocytes, whereas in the group of purpuras have been included only those cases in which the platelets were reduced. The term granulocytopenia has been reserved for those cases in which only the polymorphonuclear white cells were diminished. With the above classification in mind it is obvious that our cases of aplastic anemia include both cases of clinical purpura hemorrhagica and granulocytopenia. Our own case reports follow.

Case Reports

Case I. T. Y., age 53, white male. This patient entered the hospital on August 8, 1930, because of rapidly failing vision. He gave a history of a chancre eight years before with treatment consisting of four injections of neoarsphenamine with apparently no reactions.

Essential Physical Findings. Eyes: Argyll-Robertson pupils and primary optic atrophy in both eyes. Heart: Accentuation of both the aortic and pulmonic sec-

ond sounds. Liver and Spleen: Neither were palpable. Knee Jerks: Present only on reinforcement. A diagnosis of central nervous system syphilis was made and he was started on treatment. He received each week for four weeks an intravenous injection of old arsphenamine (0.3 gm., 0.4 gm., 0.5 gm.); intramuscular injections of bismuth salicylate 2 grains; and intraspinal injections of .0004 gms. of old arsphenamine mixed with 4 to 6 cc. of the patient's own spinal fluid. The patient suffered no reactions following the first three courses. He received his last series of injections on August 29, 1930.

Course in the Hospital. 9-1-30. Complained of marked weakness associated with pain in chest, back and abdomen. Temperature 101.4 degrees Fahrenheit.

9-3-30. A mild stomatitis which was noted late in the evening the day before had become worse and the breath was very offensive. Blood studies revealed a marked leukopenia associated with a relative monocytosis. Only an occasional polymorphonuclear cell could be found. There was a mild secondary anemia present. The temperature was 102.4°.

9-4-30. The patient became drowsy and complained of severe sore throat and dysphagia. Blood studies were again made and no polymorphonuclears were found.

9-5-30. Blood pressure dropped 10 to 15 mms. and adrenalin, minims 5, t.i.d., was commenced.

9-6-30. Throat showed a diffuse dirty gray exudate which was moderately adherent to the underlying structures. Cultures were negative for Klebs-Löffler organisms but showed a suggestive growth, presumably diphtheroids. These were repeated with similar interpretations. The patient was given 1 gm. of sodium thiosulphate intravenously.

9-7-30. In view of the suggestive positive cultures, the patient was transferred to the Contagious Hospital and given 20,000 units of diphtheria antitoxin, after which he made an uneventful recovery. He was discharged with an essentially normal blood picture on 9-25-30.

Additional Laboratory Data. The blood Kahn was positive as was that upon the cerebrospinal fluid. Agglutination tests were negative for *B. typhosus, paratyphosus A* and *B, B. abortus* and *B. melitensis.* The blood culture showed no growth. Nonprotein nitrogen determination was 36.5 mg. per 100 cc. of blood. X-ray examinations of the lungs were negative.

Discussion of Case I. In the above case there were no warning signs of arsphenamine intoxication until after the fourth injection of arsphenamine, so it is felt that the complication was unavoidable. It is unfortunate that a complete blood count was not done on entrance, for had such been done it would have been possible to know whether there was present a preexisting neutropenia. The day the patient complained of marked dysphagia and sore throat no polymorphonuclears could be demonstrated in the blood

Blood Findings in Case I

Date	W.B.C.	Polys.	Monocytes.	Lymph.	Eos.	Bas.	R.B.C.	Hgb.	Remarks
9- 3-30	2400	Rare	Predominant				4,430,000	75	
9- 4-30	3000								
	7700	0	70	12	1		3,890,000	61	
In addition there were 3% "blast" cells and 13% "mashed" cells and one atypical lymphocyte. The red blood cells were essentially normal and the platelets were slightly increased in number.									
9- 7-30									Antitoxin and sodium thiosulphate
9-10-30	5850	40	12	50	3			60	
9-17-30	4600	57	5	34	2	1			
One myelocyte was found.									

stream. Roberts and Kracke[76] have shown conclusively that there is first a bone marrow depression which is followed in a few days by a hematogenous demonstration of granulocytopenia. Three to four days may elapse even after this is discovered before the patient complains of any clinical symptoms. In view of the above, it is quite probable that the blood count would have shown a mild reduction in polymorphonuclear cells before the onset of the patient's symptoms. The patient suffered a temporary exhaustion of his granulocytes with a temporary failure at production of them. This, no doubt, predisposed him to infection with the ordinary bacterial flora, producing a rather marked stomatitis, ulcerative pharyngitis, and tonsillitis.

This case cannot be called one of aplastic anemia because there is an increase in the platelets and only mild diminution of the red blood cells; no more than one would ordinarily expect from any acute infection. It actually fits in somewhere between a granulocytopenia and aplastic anemia and is an excellent illustration of how arsphenamine can affect various combinations of bone marrow elements. The symptoms, however, as well as the clinical findings, were probably caused by the failure of the bone marrow to produce polymorphonuclear cells in sufficient numbers; and therefore this case is considered one of toxic (arsphenamine) granulocytopenia. There is no adequate explanation for the increase in the monocytes except that it is a well known fact that when for any reason the polymorphonuclear cell is unable to respond to an infection it is the monocyte that takes its place.

In spite of the negative cultures for Klebs-Löffler organisms, antitoxin was given, following which the patient commenced to improve. Whether the injection of antitoxin was coincidental with the crisis or whether it stimulated the exhausted bone marrow to further proliferation of granulocytes is impossible to state, although it is felt that the former is probably true.

Several cases have been reported in the literature paralleling the above. The one that is practically identical is that reported by Wilson.[59] Dodd and Wilkinson,[41] Moore and Foley,[7] Foster,[37] Pouzin,[39] Gougerot, Barthélemy and Uhry[27] all report cases very similar to the author's.

Case II. J. M., age 19, white female. This patient entered the Department of Dermatology and Syphilology on Feb. 20, 1931, with active secondary syphilis. She had had no previous antisyphilitic treatment. Physical examination revealed in addition to a follicular and maculo-papular syphilide, a palpable spleen. The rest of the physical examination was negative with the exception of some tenderness in the left lower quadrant caused from a pelvic inflammatory disease. Laboratory findings were negative on entrance.

Treatment: 2-20-31. Intravenous injection No. 1, arsphenamine, .3 gm.
Intramuscular injection No. 1, bismuth salicylate, grains 2.
No reaction.
2-24-31. Intravenous injection No. 2, arsphenamine, .4 gm.
No reaction.
2-25-31. Intravenous injection No. 3, arsphenamine, .5 gm.

Course in the Hospital. Two days follow-

ing the last injection the patient became nauseated, vomited, and complained of pain in her left lower quadrant. Her temperature was 102 degrees. Six hours later the temperature rose to 104°. A blood count revealed 7200 white blood cells and 70 per cent polymorphonuclear cells. On March 1, 1931, the patient presented a toxic erythema. She was placed on sodium thiosulphate daily, forcing of fluids, saline catharsis and alkalinization. For the next six or seven days she ran a very stormy course; her temperature continued to climb, reaching as high as 107°. Hypodermoclysis, protoclysis, and intravenous glucose were resorted to. On March 8 rather marked improvement was noted; the edema of the face, which had appeared conjointly with the toxic erythema, began to disappear, as did also the rash. The next day, however, the blood examination revealed a marked granulocytopenia, and the patient complained of sore gums. Examination, however, revealed no ulcerations or hemorrhage. Twenty-four hours later no polymorphonuclears could be demonstrated in the blood stream. From March 10 to March 18 the patient received three transfusions of whole blood. The appetite commenced to improve, as did the blood picture. With the reappearance of the polymorphonuclears in the blood stream there was a disappearance of the sore gums. There developed at this time a thrombophlebitis in the left arm and many subcutaneous perineal abscesses necessitating drainage. Examination of the pus revealed numerous cocci and several newly-forming polymorphonuclear leukocytes. On March 30 her condition had improved to such an extent that she was given her second injection of bismuth salicylate. She made an uneventful recovery and was discharged on April 5, 1931.

Summary. The above case is that of a young girl who, the day following her third injection of old arsphenamine, developed a high fever associated with abdominal pain which was followed in a few days by a toxic erythema. At the onset of this condition her blood picture was normal but there soon developed a picture of granulocytopenia associated with sore gums, but not accompanied by ulcerations or hemorrhage. She ran a very stormy course, but after treatment consisting of daily injections of sodium thiosulphate, forcing of fluids, alkalinization, liver extract, local mouth antiseptics, and frequent small blood transfusions, she recovered sufficiently to be discharged 39 days after the onset of symptoms.

Blood Findings in Case II

Date	R.B.C.	W.B.C.	Hgb.	Plat.	Diff.		Remarks
2/20/31	5,070,000	9500	85%	Normal	Polymorphonuclears	54%	
					Small lymphocytes	5%	
					Large lymphocytes	32%	
					Monocytes	8%	
					Eosinophiles	1%	
2/26/31	4,370,000	7700	65%		Polymorphonuclears	77%	The day following last arsphenamine injection. Fever 103 degrees. Transferred to Gynecology because of pelvic pathology.
					Small lymphocytes	2%	
					Large lymphocytes	7%	
					Monocytes	7%	
					Eosinophiles	5%	
					Basophiles	2%	
2/27/31		15,000					

Blood Findings in Case II—*Continued*

Date	R.B.C.	W.B.C.	Hgb.	Plat.	Diff.		Remarks
2/28/31	4,770,000	11,900	71%				Chill. Fever 107°. No malarial parasites found in smear.
3/1/31							Sodium thiosulphate started.
3/3/31		6,800	70%		Polymorphonuclears	70%	
					Small lymphocytes	26%	
					Large lymphocytes	2%	
					Eosinophiles	2%	
3/9/31	4,420,000	2,000	73%		Polymorphonuclears	24%	Complains of sore gums.
					Small lymphocytes	45%	
					Large lymphocytes	20%	
					Eosinophiles	5%	
					Unclassified	3%	
3/10/31	3,950,000	2,600	56%	Increased	Polymorphonuclears neut.	0%	
					Large lymphocytes	30%	
					Small lymphocytes	14%	
					Monocytes	45%	
					Eosinophiles	10%	
3/11/31		3,300	76%		Polymorphonuclears	0%	1st transfusion of 300 cc. of whole blood.
					Small lymphocytes	18%	
					Large lymphocytes	4%	
					Monocytes	70%	
					Eosinophiles	2%	
3/12/31	4,860,000	2,350	73%		Polymorphonuclears	0%	
					Small lymphocytes	56%	
					Large lymphocytes	12%	
					Monocytes	28%	
					Eosinophiles	4%	
3/13/31							2nd transfusion, 450 cc.
3/14/31	4,190,000	3,150	65%		Polymorphonuclears	2%	
					Small lymphocytes	44%	
					Large lymphocytes	6%	
					Monocytes	46%	
					Eosinophiles	2%	

Blood Findings in Case II—*Continued*

Date	R.B.C.	W.B.C.	Hgb.	Plat.	Diff.		Remarks
3/18/31		5,400	84%		Polymorphonuclears	25%	3rd transfusion of 400 cc. blood.
					Small lymphocytes	30%	
					Large lymphocytes	12%	
					Monocytes	30%	
					Eosinophiles	3%	
3/20/31	5,200,000	7,100	84%		Polymorphonuclears	77%	Gums much better.
					Small lymphocytes	16%	
					Large lymphocytes	4%	
					Monocytes	9%	
					Eosinophiles	2%	
					Basophiles	2%	
3/29/31	4,540,000	7,150	78%	Increased	Polymorphonuclears	62%	
					Small lymphocytes	16%	
					Large lymphocytes	14%	
					Monocytes	2%	
					Eosinophiles	4%	
					Basophiles	2%	
4/2/31	5,320,000	10,300	94%		Polymorphonuclears	65%	
					Small lymphocytes	20%	
					Large lymphocytes	7%	
					Monocytes	6%	
					Eosinophiles	1%	
					Basophiles	1%	

Discussion of Case II. Because of the mild anemia that developed as the condition progressed, this case, from the blood picture, is one of aplastic anemia. However, clinically it is considered one of toxic granulocytopenia for reasons similar to those in our first case. Prior to the onset of the patient's granulocytopenia, she suffered a not uncommon toxic reaction from arsphenamine, characterized by a toxic erythema, fever, vomiting and chills. At the onset the blood picture was normal, and at this time the patient did not complain of any sore gums, or subcutaneous abscesses. However, as soon as she did, blood studies revealed a total absence of polymorphonuclear cells. Coincident with the return of the granulocytes to the blood stream, there was marked subjective and clinical improvement in the condition about the gums. The fact that granular white cells were found in the pus from the perineal abscesses may be considered an earlier sign for predicting improvement than the blood studies. Recovery in this case was no doubt materially aided by the intravenous injections of sodium thio-

sulphate and frequent small blood transfusions.

Case III. M. D., female, aged 26. Entered the University Hospital March 31, 1931, because of severe swelling of the face, legs, sore mouth and sore throat. This condition started 10 days before her admission and 24 hours after her fourth weekly injection of neoarsphenamine (0.75 gm., 0.9 gm., 0.9 gm., 0.9 gm.) for primary syphilis. She had run a fever of 101° to 103° F. but had had no chills or jaundice. The patient had been a known and treated diabetic for the past nine years. Her mother is said to have pernicious anemia. There was no history of any hemorrhagic tendency.

Essential Physical Findings on Entrance. The patient was dull and apathetic and gave every evidence of being acutely ill. The entire mouth was inflamed and the gums were so tender that it was impossible to make a thorough oral examination. A few superficial ulcerations were noted about the lips and tongue. There was a blowing systolic murmur heard at the apex. The abdomen was slightly distended. The liver and spleen were not palpable. The right ankle and tibial area showed pitting edema. Vaginal examination and rectal examination revealed no ulcerations.

Laboratory Findings on Entrance. Blood: W.B.C., 600; R. B. C., 4,100,000; Hgb., 80% (Sahli). Only one white cell was seen in 15 minutes examination of the stained smear. Urine: Trace of albumin; 3 plus sugar; 1 plus diacetic acid; 1 plus acetone. Kahn test: Neg. (repeatedly).

Course in the Hospital: On admission the patient's temperature was 103°, pulse 120, and respirations 20. Her condition seemed to be quite serious and she was immediately given a transfusion of 500 cc. of blood. The following day she appeared somewhat better and was placed on a soft diabetic diet, without insulin. She was given sodium perborate and warm saline mouth irrigations, alternating each hour. From this time on, she was given daily intravenous injections of sodium thiosulphate in one gram doses. She was also given adenine sulphate in doses of 0.5 gram every other day, intravenously. It was difficult to get the adenine sulphate into solution. Normal 1/10 hydrochloric acid was finally necessary and the first dose of adenine was given by mouth, because of the fear of giving 1/10 normal hydrochloric acid intravenously. It was discovered, however, that the solution could be satisfactorily buffered, and although this brought about a milky precipitate of the adenine, nevertheless given intravenously it caused no reaction. She was given every other day small blood transfusions of 250 cc. Daily white blood counts showed a small peak, the rise being on April 6, when a count of 1300 was reached. The patient's diabetes was well controlled without insulin until April 7 when she showed 4 plus sugar and 3 to 4 plus diacetic acid in all specimens. She was consequently placed on insulin, 16 units 3 times a day, which kept her sugar free. The patient seemed to show definite improvement symptomatically. The swelling and pain went down remarkably; she became brighter and the extreme soreness of her mouth diminished. Re-examination of the mouth on several occasions showed large quarter-dollar sized sloughing areas, on the lateral pharyngeal wall of each side. The patient continued to run an elevated temeprature, as high as 104°. There had been no startling changes in the white blood count. There was, however, symptomatic improvement until the morning of April 10, when the patient suddenly complained of severe generalized abdominal pain, associated with severe distension which could not be relieved by the ordinary measures. Since some form of intestinal obstruction seemed obvious, she was seen in the Department of Surgery. It was felt that in view of her other conditions a laparotomy was not warranted. From this time her course was steadily downhill. The skin assumed a definite icteric tint which increased markedly until death. The conjunctivae which were clear previously also became icteric. The white blood cell count dropped, and on March 11 was 500 cells per c. mm. Her lung fields remained clear until the morning of that day when numerous coarse moist râles were heard in each lung base, asso-

ciated with a friction rub. The patient died at 2:30 P.M., March 11, 1931.

Diagnosis at Autopsy. "Agranulocytosis". Multiple necroses and early ulcers of tongue, pharyngeal tonsils, transverse colon and rectum. Sub-acute adhesive peritonitis with acute fibrinous peritonitis superimposed Localized necrotizing perisplenitis. Early pyemic abscesses in spleen. Acute hyperplastic mesenteric and retroperitoneal lymphadenitis. Congested aplastic bone marrow. Encapsulated tubercles in bronchial lymph nodes. Subendocardial fatty degenerative infiltration. Acute passive congestion and parenchymatous degeneration of all organs.

Blood Studies

Date	R.B.C.	W.B.C.	Hgb.	Diff.	Remarks
3-31-31	4,150,000	600	67%		Practically all white cells are lymphocytes, but so few that a differential is impossible.
4- 1-31	5,270,000	750	80%		As above
4- 2-31		500			
4- 2-31		700			
4- 2-31		600			
4- 2-31		450			
4- 3-31	4,400,000	650	70%		32 lymphocytes and 2 polymorphonuclears on entire smear.
		850			
4- 4-31		750			Lymphocytes predominate.
		950			Lymphocytes predominate.
4- 6-31		950			
		1150			
4- 6-31		1300			
4- 7-31		1200			
		900			
4- 8-31		650			
		850			
4- 9-31		750			Lymphocytes predominate.
	5,060,000	900	93%		

Additional Laboratory Data. Urine showed 2 to 3 plus sugar practically continually. Highest blood sugar, 243 mg. per 100 cc. on March 31, 1931. Blood NPN 31.9 per 100 cc. Blood chlorides 357 per 100 cc. whole blood. Culture from throat showed a bacillus morphologically typical of *B. diphtheriae*.

Discussion of Case III. This case fits in classically with Schultz's description of agranulocytic angina except that here arsphenamine was no doubt the inciting etiological agent. The apparently normal red blood count and hemoglobin, together with a marked leukopenia and absence of polymorphonuclears, make this case one of true granulocytopenia. To our knowledge this is the first case of this type due to arsphenamine in which the nucleotide therapy described by Reznikoff[38] has been employed. It is interesting to note again the occurrence of diphtheria-like organisms in cultures from the throat. These findings are not new. Baldridge and Needles[35] found similar organisms in cultures from one of their cases. These findings, however, are not believed to be of any great significance.

There is a close similarity in this case to the first two. The essential differences are that in this case there is more of a selective action on the granulocytes, as well as a longer period of depression than in cases I and II. The bone marrow became so exhausted that it was unable to function. With the disappearance of granulocytes from the blood stream and bone

marrow, the patient's immunity was greatly lowered and her resistance to infection was overcome. Thus there developed a stomatitis with extensive ulcerations and an ultimate fatal outcome. In short, as Roberts and Kracke[78] have shown, life is not compatible with an absence or granulocytes.

Our pathologist stated that he had never before seen such an extensive necrotizing process in a case of granulocytopenia as existed here, and no mention of such an extensive process was found in the review of the literature. Some pathologists, no doubt, would not consider this case one resulting from arsphenamine intoxication because no chemical evidence of arsenic was detected and the liver was not that of arsenical hepatitis. The present post-mortem chemical tests for arsenic were not considered sufficiently accurate to bear weight either way, and therefore were not employed. Perhaps the arsenic was stored exclusively in the bone marrow, thus accounting for the blood dyscrasia and absence of any arsenical hepatitis. Cases of bone marrow depression are too numerous in the literature for them to be mere accidental findings, and thus there is no hesitancy in recording this as another one in spite of the failure to find certain classical signs of arsenical intoxication.

Case IV. B. W., female, age 23. This patient entered the hospital December 19, 1929, complaining of weakness, bleeding from the gums and vagina, and marked fatigue. Six years before entrance she had had a primary syphilitic lesion. She was under constant treatment with neoarsphenamine and the heavy metals until three months before, at which time she entered a Detroit hospital. The last injection of neoarsphenamine was 10 months prior to the onset of her symptoms. The exact number of injections is not known, but she stated that she had at least 50 injections of meoarsphenamine, together with bismuth, mercury and Bismarsen.

Essential Physical Findings. The patient was a pale undernourished woman who was mildly icteric. The tonsils were moderately enlarged. There was evidence of old hemorrhage at the gum margins and also a black line was present. The spleen was not felt. The liver was thought to be just palpable below the coastal margin.

Blood Findings on Admission. R.B.C., 1,470,000; W.B.C., 2000; Hgb., 22%. Differential: polymorphonuclears, 33%; large lymphocytes, 26%; small lymphocytes, 34%; monocytes, 6%; eosinophiles, 1%.

Blood Kahn, negative. Urinalysis, negative.

A diagnosis of aplastic anemia following neoarsphenamine was made.

Course in the Hospital. Dec. 23. The patient was started on adrenalin 0.4 cc. (This was increased daily until 0.7 cc. was given, after which she was maintained on this dose.) She was also placed on a high vitamin diet.

Dec. 27. A transfusion of 500 cc. of citrated blood was given. Following this the temperature went to 102° and she complained of pain in the epigastrium.

Jan. 3. Another transfusion of 500 cc. of blood given.

Jan. 16. The patient has maintained her blood condition fairly well since the last transfusion. Bleeding from gums and nose noted.

Jan. 23. Still bleeding from mucous membranes. The spleen was felt about an inch below the costal margin.

Jan. 29. Transfusion of 400 cc. of citrated blood. Temperature rose to 103°.

Feb. 3. Ventriculin was started (10 grams daily).

Feb. 25. Still bleeding occasionally. The condition is about the same.

March 6. Vaginal bleeding noted. Condition, however, improved.

March 9. Discharged.

Since the patient's discharge she has returned frequently for observation, and when

this has been impossible she has had blood counts taken and notified us of the results. In this way it has been possible to follow her until September 2, 1930, at which time she complained again of weakness, nervousness, and insomnia.

Numerous blood studies were made, but only part of them are included below:

Blood Findings in Case IV

Date	R.B.C.	W.B.C.	Hgb.	Diff.	Reticulocytes	Remarks
*10-11-29	1,280,000	2400	20%	Polymorphonuclears 43% Small monocytes 57% Large monocytes 0%		
*10-23-29	1,370,000	3050	30%	Polymorphonuclears 48% Small monocytes 45% Large monocytes 6%	.6%	
12-20-29	1,470,000	2000	22%	Polymorphonuclears 33% Eosinophiles 1% Large lymphocytes 26% Small lypmocytes 34% Monocytes 6%		Platelets markedly diminished
12-24-29	1,200,000	3850	19%		.1%	
12-27-29	1,280,000	3650	18%		.1%	Transfused.
12-28-29	1,970,000	3200	23%		.1%	
1- 3-30	1,910,000	3150	23%		.5%	Transfused.
1- 4-30	2,680,000	3700	36%		.8%	
1-29-30	1,460,000	2750	20%		1.5%	Transfused.
1-30-30	2,050,000	3600	31%		2.1%	
2- 3-30	1,820,000	4150	30%		3.0%	Started ventriculin 10 gm. daily.
2-19-30	1,220,000	2900	27%		8.1%	
3- 6-30	1,330,000	4150	32%		6. %	
3- 9-30						Discharged.
4-10-30	2,250,000	5300	49%	Polymorphonuclears 66% Lymphocytes 44%		
5-14-30	3,500,000	5200	75%			
9- 2-30	2,616,000	5800	72%	Polymorphonuclears 54% Lymphocytes 44% Endothelial cells 2%		

*These two counts were made prior to entrance.

Case Summary. Case IV is that of a young woman who four months after her last neoarsphenamine injection developed marked weakness and vaginal bleeding. On entrance to the University Hospital she presented a typical blood picture of aplastic anemia. She remained in the hospital three months, during which time she had several hemorrhages. She received in the form of treatment transfusions, adrenalin, ventriculin, ammonium chloride and calcium lactate. The last blood count was made six months after her discharge and at this time there was still present a blood picture of aplastic anemia and the patient was complaining of weakness, nervousness and insomnia.

Discussion of Case IV. In this case we have all the elements of the bone marrow depressed, and hence from the blood findings, it is an example of aplastic anemia. Clinically it cannot be called a case of purpura hemorrhagica, in spite of the marked hemorrhages because no purpuric spots or petechiae were found. The neoarsphenamine was no doubt the inciting toxic agent that produced the particular blood dyscrasia. However, it is probable that the patient possessed a predisposed hemopoietic weakness upon which the neoarsphenamine could act, and that there was a marked thrombocytopoietic idiosyncracy, thus accounting for the signs and symptoms of hemorrhage.

Case V. J. C., white male, age 33. This patient gave a history of a primary sore five years before for which he was given local therapy. Seven months before his second course of neoarsphenamine he received a first course consisting of eight injections, accompanied by an equal number of injections of a heavy metal. He apparently suffered no reactions. His second series of injections were made in a nearby city and consisted of four neoarsphenamines, 0.6 gms.; two, 0.75 gm., and two, 0.9 gm., along with nine injections of mercury salicylate intramuscularly. Following the fifth injection of neoarsphenamine he developed a sore mouth and noticed that ecchymoses developed at the previous site of injection; following the sixth injection a similar extravasation of blood was noted at the point of entrance into the vein. A few days later he developed a toxic rash. Following his last two injections (seventh and eighth), he was so weak and dizzy that he had to lie down for several minutes. Three days prior to his entrance to the University Hospital he noted hematuria.

Essential Physical Findings on Entrance. The patient was a decidedly ill, undernourished man of 35. The gums were swollen, bleeding, and many purpuric patches were present on the skin. There was hemorrhage from the nose. Hemorrhagic verrucous papules were present on the tongue and buccal mucosae. The liver was felt three fingerbreadths below the costal margin. The spleen edge could not be definitely made out though some resistance was noted. The skin was mottled with petechiae and ecchymoses.

Essential Laboratory Findings on Admission. Blood: R.B.C., 2,330,000; W.B.C., 11,500; Hgb., 46%. Bleeding time, 18 minutes. Stool: Grossly bloody. Urine: Few red blood cell casts. 200 R.B.C. per low power field. Trace of albumin.

The Kahn test was negative, but the presumptive Kahn test was positive.

Course in the Hospital. (Taken from ward notes made by attending physician.)

10-10-29. Patient admitted to the ward with a diagnosis of purpura following antisyphilitic therapy. Started on forced fluids, calcium gluconate, alkalinization, sodium thiosulphate intravenously (1 gm.), daily catharsis, coagulin subcutaneously. Had a fairly good day. Temperature 99.4° F.

10-11-29. Small amount of bleeding from the gums. Transfused with 525 cc. of citrated blood. Fever, 100°. Given 1 gm. of sodium thiosulphate.

10-12-29. Condition about the same. Sodium thiosulphate, 1 gm. intravenously. Coagulin, 1 cc. given subcutaneously. Fever 101°.

10-13-29. Considerable bleeding from

nose and mouth. Coagulin given. Sodium thiosulphate, 1 gm., given intravenously.

10-14-29. Condition unchanged. Sodium thiosulphate given.

10-15-29. No bleeding from the mouth until late in the evening.

10-16-29. Emesis of dark, foul smelling fluid. Weaker. Nauseated. Transfused with 650 cc.

10-17-29. Small clots of blood expectorated. Complains of severe headache. Drowsy and sleeps at long intervals. Temperature normal.

10-18-29. Condition unchanged.

10-19-29. Disoriented. Found lying on the floor. Pulse 48. Patient is cold. Much weaker.

10-20-29. Still bleeding from the gums. Breath foul. Incontinent. Stuporous. Respirations labored. Temperature 100, pulse 80, respirations 24. Respirations ceased at 11:25 A. M.

Necropsy Findings. Hemorrhagic diathesis of toxic origin (arsenic, mercury, bismuth?). Hemorrhagic necrotic encephalitis. Multiple hemorrhages into the brain substance, meninges, subcutaneous tissue, gastric mucosa and subepicardial tissue, with hematomata in both renal pelves. Anemia. Acute parenchymatous degeneration of all organs. Fatty degenerative infiltration of liver. Subepicardial fatty infiltration. Active caseating tubercle in the bronchial lymph nodes. Multiple caseating tubercles in the spleen and liver. Hemorrhagic adenoma in the left lobe of the thyroid. Syphilitic aortitis. Atrophic scar on penis. Old syphilis. Bone marrow slightly hyperplastic. Few megakaryocytes. Marrow smear shows diminution in red cell line and very few megakaryocytes. Numerous normoblasts. Very few megaloblasts.

Summary. In case V we have the case of a young man, who, after having received 13 injections of neoarsphenamine, developed signs of intoxication and intolerance to the drug evidenced by ecchymoses and petechiae. He was given three more injections following which he became worse and commenced bleeding from the mucous membranes. When admitted to the University Hospital he showed evidence of the above process. Blood counts revealed a normal differential count, total absence of platelets, a moderate anemia, an increased bleeding time, and normal clotting time. In spite of transfusions and sodium thiosulphate the patient died on his tenth day in the hospital.

Blood Findings in Case V

Date	R.B.C.	W.B.C.	Hgb.	Platelets	Differential	Remarks
10-10-29	2,330,000	11,500	46%	Absent	Polymorphonuclears 76% Lymphocytes 14% Monocytes 4% Eosinophiles 6%	Bleeding time, 18 minutes. Clotting time normal.
10-11-29						525 cc. blood transfused.
10-15-29	1,960,000	11,150	33%	Absent	Polymorphonuclears 66% Lymphocytes 24% Monocytes 6% Eosinophiles 3% Basophiles 1%	
10-17-29	2,830,000	14,500	50%	Occasional		Transfused 650 cc. 1 reticulocyte seen.
10-18-29	3,420,000	13,300	55%	Rare		
10-19-29	2,850,000	18,450	51%			

Discussion of Case V

This is a typical example of purpura hemorrhagica, thus completing in this series of cases those illustrating the effect of the arsphenamines on each individual element of the bone marrow. This case cannot be called a toxic aplastic anemia in spite of the fact that there was a marked secondary type of anemia along with marked diminution of the platelets, because there was no apparent failure in the production of polymorphonuclear cells.

In the above case there were sufficient warning signs of intolerance to the drug to warrant discontinuing further therapy, and it is to be regretted that further arsphenamine was used after the appearance of these symptoms. Had immediate treatment been instituted following the first signs of intoxication the prognosis for recovery would no doubt have been greatly enhanced. Treatment, in spite of transfusions and sodium thiosulphate, proved inadequate, and the patient died, not of an aplasia of the bone marrow, nor as a result of infection, but rather because of hemorrhage. Necropsy substantiated this evidence when it showed a hyperplastic bone marrow with a diminution of the red cell line, together with multiple visceral hemorrhages. Death was no doubt due to a hemorrhagic encephalitis.

General Discussions

Perhaps one of the most confusing and interesting problems to confront in these cases of post-arsphenamine blood dyscrasias is the etiological factor concerned. Some authors contend that it is the organic arsenic factor that is responsible, whereas others feel that it is the benzol radical; few take the attitude that both are responsible. Lawson, Jackson, and Cattanach[2] in reporting 28 cases of inorganic arsenic poisoning have shown that inorganic arsenic may produce a marked diminution of polymorphonuclear leukocytes with a relative monocytosis. In their cases there was, in addition, a marked lowering of the platelet count and in several patients there were symptoms of gross intestinal bleeding as evidenced by bloody stools. In one case there was also a rather severe epistaxis. Wheelihan [42] three years later reported a case of granulocytic aplasia of the bone marrow following injections of potassium arsenite in a child.

Organic arsenic obviously produces various types of bone marrow depression, as is shown by numerous cases, including the author's.

Benzol is known to produce both a neutropenia accompanied by symptoms of marked sore throat, as shown by Rohner, Baldridge and Hansmann,[1] as well as purpura and aplastic anemia as shown by the same authors and also McCord,[47 48], Sweeney, [49] and Selling.[8]

It appears then from such an analysis that no one drug is entirely responsible for all cases of bone marrow depression. Inorganic arsenic has been employed in medical therapeutics for centuries, but until Lawson, Jackson and Cattanach[2] reported their cases in 1925, the literature failed to reveal any cases illustrating its toxic effect on the bone marrow. Prior to Evans[58] report in 1916 no cases were found in the literature illustrating the effect of organic arsenic on the bone marrow.

Sepsis, infection, irradiation, and chemicals are each known to produce depression of the bone marrow. There are other factors to be considered, however, for otherwise blood dyscrasias following the arsphenamines would occur more frequently. It is suggested that a predisposed, weakened, hematopoietic apparatus is probably of great importance as a secondary factor in every case of bone marrow depression. There is, however, still another factor to be considered as playing a rôle in the etiology of these diseases, and this is one heretofore entirely overlooked; namely, the syphilitic infection itself. There is at present no pathological evidence to indicate that these blood dyscrasias are due to actual invasion of the bone marrow by the spirochete, yet a syphilotoxic action should always be kept in mind as a possibility.

In addition to the etiological factors mentioned above might be mentioned drug idiosyncrasy, which is supported by the fact that one form of arsphenamine may be rather well tolerated, but when one shifts to another form (as from old arsphenamine to one of the neoarsphenamine preparations), symptoms of toxicity occur.

Inorganic arsenic, organic arsenic, and benzol, then, all play a share in producing bone marrow depression. Any drug that combines more than one of the above compounds, as do the arsphenamines, probably plays a greater rôle as an etiological agent than any of the drugs individually.

Among the organic arsenicals responsible for granulocytopenia, purpura, and aplastic anemia, neoarsphenamine is the greatest offender. In our clinic, however, this was not true; both cases followed injections of old arsphenamine. It is possible that the explanation of this lies in the fact that in our clinic more of the old arsphenamine is employed than any of the other arsphenamine preparations.

Due to a certain lack of fundamental knowledge concerning the exact function of the bone marrow elements, it is hardly possible to make an accurate classification of diseases of the bone marrow with regard to etiological agents concerned. Certainly it is not within the scope of this paper to attempt such a thing in detail. However, for the sake of clarification, a rather simple classification which is in no way complete may be mentioned.

The arsphenamines may attack any or all of the elements of the bone marrow. If the platelets alone are depressed we get symptoms of purpura, and depending upon the degree of intoxication we get either simple purpura, purpura with hemorrhage, or, should other elements of the bone marrow be affected, purpura associated with aplastic anemia. Chemical toxicity is not the chief offender, for it is well known that purpura often results from other forms of toxicity, as well as from sepsis or bacterial infection. There might also be mentioned an idiopathic group.

The red blood cells when depressed are usually accompanied by a depression of platelets, polymorphonuclear leukocytes, or all three.

When the granulocytic element of the bone marrow alone is depressed, there results a true granulocytopenia. This likewise can be caused by chemicals, infections, irradiation, and sepsis. To this also must be added the idio-

pathic group. It is in this latter group only that the agranulocytic angina of Schultz should be placed.

If the circulating toxin, infectious products, or other etiological factors depress all three bone marrow elements; namely, platelets, red blood cells and polymorphonuclear leukocytes, a picture of aplastic anemia results.

Thus, with the above in mind, it is seen that in our cases reported the arsphenamines have acted on each of the individual elements concerned. To summarize, arsphenamine may depress either the red blood cells, platelets, polymorphonuclear cells, or any combination of these.

Treatment

In general treatment may be divided into two main divisions; namely, prophylactic and specific. The former is by far the more important. It was amazing in reviewing the literature to note the frequency with which treatment was continued after such gross clinical findings as bleeding from the gums, petechiae, membraneous sore throat, and toxic erythema. It is much wiser to refrain entirely from the further use of arsphenamine after the appearance of such signs and symptoms and to continue therapy with one of the heavy metals. Occasionally, however, it is a safe procedure to allow the patient to have a rest period of three to six months following the employment of the arsphenamine preparation, and then start in again with smaller doses of a different arsphenamine preparation.

Moore and Keidel[52] have shown that often a mild neutropenia exists after such signs and symptoms as dermatitis exfoliativa, itching, stomatitis, and purpura, and they recommend complete blood studies before continuing any form of active therapy.

At present there is no specific treatment for any of the toxic reactions resulting from the arsphenamines, but regardless of other types of therapy employed, sodium thiosulphate, one gram daily intravenously, and frequent small blood transfusions, 250 to 300 cc. three to four times a week, have been found of definite value in this clinic. There has been no opportunity in our clinic for employing immuno-transfusions; that is, blood from an individual who has recovered from the condition of which the patient is a victim. This, perhaps, offers possibilities and wherever convenient and safe should be employed.

Conclusions

1. Five cases of various types of bone marrow depression following the arsphenamines are reported and discussed.

2. The term 'agranulocytic angina' is inadequate and misleading. It is suggested that granulocytopenia is a better term.

3. Inorganic arsenic, organic arsenic and benzol may each depress any or all of the elements of the bone marrow.

4. In the blood dyscrasias following the arsphenamines, the arsenic and benzol radicals are probably both responsible.

5. A predisposed hematopoietic weakness or insufficiency which in any case may be erythropoietic, thrombocytopoietic, granulocytopoietic, or any

combination of these, is perhaps an important secondary factor in the etiology of diseases of the bone marrow following arsphenamine administration.

6. A syphilotoxic factor affecting the bone marrow is suggested as a possibility in the etiology of the blood dyscrasias in syphilitics.

7. The most adequate treatment is prophylactic. Sodium thiosulphate and frequent small blood transfusions offer the best means at present for combating the condition.

For the privilege of presenting this paper and for many valuable suggestions, I am indebted to my chief, Dr. Udo J. Wile.

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Ascending Paralysis Resulting from the Drinking of "Jamaica Ginger"; a Clinical Study of Fifty Cases*

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Paralysis resulting from the drinking of Jamaica ginger has recently presented itself in and around Los Angeles. Two hundred cases have been reported to date (March 1, 1931). This disease has been well studied and reported by various other observers since its first appearance one year ago in the Middle West and South. The cases occurring in the present so-called "epidemic" as encountered in this hospital† presented certain findings which differed from those of other authors as well as several new features which have not previously been described. In spite of a variable clinical history, the neurological findings are remarkably constant. Fifty cases have been studied in an attempt to learn more about the manifestations of the disease, and are herewith reported. An attempt has been made to emphasize the difference in the findings in my series from those already reported.

Review of the Literature

In reporting ten cases from the South, Bennett[1] considered the etiology obscure. All of his patients were corn-whisky drinkers and had taken in addition Jamaica ginger. Of particular interest was a wide variation in the time of onset of the symptoms (3 to 42 days), and the presence of hyperactive patellar reflexes associated with absent plantar reflexes. In Bennett's opinion the disease was a type of Landry's paralysis. Harris[2] reported several cases occurring in an isolated village of 100 people. The findings in these cases were similar to those in Bennett's, and he suggested that the etiological factor was some recent change in the ingredients of the ginger, probably one of the higher alcohols.

Wilson[3] reported a case in which the pupils were unequal, abdominal reflexes decreased but present and the Achilles' reflexes lost. He stressed the impairment of deep pain and vibration sense in the lower extremities. Although no visual disturbances were found in his case, Wilson referred to the cases of Thompson[4] (1897) and Woods[5] (1899) in which amblyopia resulted from ginger drinking. Goldfain[6] emphasized the absence of Achilles' reflexes and complete loss of vibration sense in the toes with only partial loss in the legs. With the exception of the first, none of these findings was obtained in this series.

The pathology of the disease has been completely studied in the few

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fatal cases by Vonderahe,[7] Jeter[8] and Goodale and Humphreys.[9] Vonderahe studied three fatal cases, one being uncomplicated by any other disease. The principal changes as he found them consisted of:

1. Progressive changes in the anterior horn cells, characterized by swelling, chromatolysis and shrinking of the cell. Ventral root fibers showed degeneration of myelin sheath and axis cylinders;

2. Only slight involvement of the posterior horn cells;

3. Severe cellular degeneration in the hypoglossal and vagus nuclei and nucleus ambiguous.

Vonderahe felt that the toxin is non-infectious, first reaching the peripheral nerves, and from these traveling through the cord to the medulla. Jeter found an exudate of lymphocytes, a few polymorphonuclear cells, much engorgement of the vessels with red cells, and small deposits of fibrin in the cauda equina. His most constant finding was a fibrosis or thickening of the interstitial structure, especially the meninges of the cord, the peripheral nerves and the perineurium.

Goodale and Humphreys studied 62 patients with "Jamaica ginger paralysis" and reported the pathology in three cases. They often found fine red-brown granules in peripheral and perinuclear situations in the cytoplasm of the nerve cells. The nucleolus was frequently absent. Focal degeneration of myelin sheaths was observed only in isolated situations. The external popliteal nerve was most frequently affected, but no changes were found in any of the nerves above the gluteal fold.

Etiology

The etiology of the disease has been definitely worked out by Smith and Elvove[10] who determined without doubt that triorthocresyl phosphate caused the degeneration of the myelin sheath, the axis cylinders and motor cells in the patients who were paralyzed in previous "epidemics." This compound is a stable combination of a phenol with a phosphoric acid ester, and was present in a concentration of about two per cent in the suspected "Jamaica ginger." Triorthocresyl phosphate has produced the identical clinical picture when given in small doses to rabbits, monkeys and calves.[10] It has been suggested that the difference in susceptibility between rabbits and monkeys, and among different people was due to variations in degree of absorbability of the phosphate from the intestinal tract.

Relation of Amount of Jamaica Ginger Consumed to the Course and Severity of the Paralysis

All of the patients here studied were of the lower and middle classes of people such as one finds in a general hospital. The average age was 49.6 years which was considerably higher than that given by Harris (between 20 and 40 years). Only three patients were women. A large majority were chronic users of alcohol. Accepting the statements of the patients, 5 were heavy drinkers, 25 were moderate drinkers, and 15 were light drinkers of alcohol. The remaining 5 patients were not chronic alcoholics and had taken no alcohol other than that in the Jamaica ginger. Most of these victims had been using alcohol either just before or with

the ginger, as follows: 11 had been drinking heavily, 9 moderately, and 13 lightly. Seventeen patients had taken no beverage other than the ginger.

Jamaica ginger causing paralysis in the present epidemic was found to contain the same poison as was found previously by Smith and Elvove. The ginger is sold in two or three ounce bottles and is taken principally for its high alcoholic content (80 per cent). When mixed with about four parts of water it is supposed to produce the usual "stimulating" effects of alcohol. Some mix it with other forms of liquor and a few take it as a "sobering-up medicine" after an alcoholic debauch. Two of the three women in the series had taken the ginger for dysmenorrhea. Most of the patients were not habitual users of "Jake," having used it only one or two times before the onset of symptoms. However, 13 patients were habitual ginger drinkers. The amount of beverage consumed in these cases is indicated by the following:

One	patient	had taken	12	bottles per month	for	10 years.
One	patient	had taken	2	bottles per day	for	3 years.
Three	patients	had taken	2	bottles per day	for	6 months.
One	patient	had taken	4	bottles per week	for	6 months.
One	patient	had taken	1	bottles per day	for	1 month.
One	patient	had taken	2	bottles per month	for an indefinite time.	
One	patient	had taken	6	bottles per week	for an indefinite time.	
One	patient	had taken	3	bottles per week	for an indefinite time.	
One	patient	had taken	2	bottles per week	for an indefinite time.	

In the study of these cases one was soon impressed by the great variation in the onset and course of the disease, whereupon an attempt was made to learn the relation between:

1. The amount and duration of the Jamaica ginger drinking;

2. The time between the drinking and the onset of the symptoms, i.e., "latent period"; and finally,

3. The extent and degree of the paralysis.

The Amount and Duration of Drinking

The average number of two-ounce bottles ingested by the patients in this series was 5.5, and the average number of days in which they were consumed just prior to the onset of symptoms was 5.3, making the combined average about one bottle per day for five days. This includes four cases in which only one bottle was taken, and eleven in which two were taken. These figures are not given to show the amount of contaminated ginger necessary to cause the disease, but only to indicate the extent of the drinking in this series. The assumption that patients absorb different amounts of the poison from the intestinal tract, as proposed by Smith and Elvove, makes it difficult to say how much of the phosphate is needed to cause the paralysis. We know that with some patients as little as one two-ounce bottle contains enough triorthocresyl phosphate to produce extensive degeneration in the peripheral nervous system.

Period of Onset

There have been different estimates regarding the number of days constituting the "latent period" of the disease. For patients having taken one

or two bottles in one or two days, the average time before the onset was 5.2 days, while the "latent period" for patients having taken from six to twenty bottles within seven days was 12.1 days. From these figures alone one would conclude that the more ginger taken the slower the onset; or that the patient works up a resistance to the poison; or perhaps that the cramps and weakness do not occur while the drinking is in progress. However, I am inclined to believe that the discrepancy is due to the fact that the patient who has been drinking for several days does not know just which of the suspected bottles of ginger contained the toxic element, and on what day he began taking the contaminated ginger. Therefore little reliance can be placed upon the history in this regard. This point is particularly well proven by the fact that in the series in which there was a large amount of ginger taken the average number of days from the drinking of the *last* bottle of Jamaica ginger to the onset of symptoms was 5.5 days. This last figure corresponds closely with the 5.2 days between the ingestion of only a *small* amount of poison and the onset of the first symptoms. However, here again one can only generalize in his conclusions, for in several cases from 22 to 29 days elapsed before the first symptoms appeared.

Extent of Paralysis

It is also difficult to estimate the relation between the amount of ginger taken and the extent of the nervous system destruction, but an attempt is made to do so by comparing the number of patients with complete loss of motor power and deep and superficial reflexes in a series of patients (10) who had consumed large amounts of ginger (6 to 20 bottles) with a similar series of patients (20) who had used only small amounts of ginger (1 to 3 bottles).

In those patients who had taken a much larger amount of poison, I have observed that:

1. Motor power of the legs and the tendo Achilles' reflexes (L IV to S III), being already markedly impaired in nearly all cases having taken only small amounts of ginger, show no further loss.

2. Motor power of the quadriceps femoris, the patellar reflex (L II-IV) and the cremaster reflex (L I) are lost in twice as many cases.

3. Biceps reflex (C V, VI) is lost in 4 times as many cases.

4. Flexion of the wrist (C VI-TI) in 4 times as many cases.

These observations show that the degeneration is an ascending one, the height of which is somewhat proportional to the amount of triorthocresyl phosphate absorbed by the patient. Vonderahe[7] came to the same conclusion after studying the cells in the motor nuclei of the medulla. One of our patients, a woman of 32 years, had all the findings of a degeneration which had ascended as high as the cervical cord. Abdominal and biceps reflexes were absent, and there was a complete loss of function of the hands and forearms. Fifteen days following her first symptom, she developed an aphonia and for three weeks could not speak above a whisper. Laryngoscopic examination revealed the vocal cords to be fixed in partial adduction.

Her pulse rate while lying quietly in bed varied from 60 to 120 per minute.

Symptomatology

Cramps, soreness and stiffness of the calves of the legs were the first symptoms in the majority (33) of the cases. About one-fourth of the patients also experienced weakness of the feet and legs at the same time; however, in most of the cases, weakness came on three days later. Sensory changes were conspicuously absent in all but three cases. The "dead" feeling of the feet described by many of the patients was found, on further questioning, to refer to loss of motion rather than to any sensory loss. Cramps of the calves of the legs occurred alone in fifteen cases, were accompanied by soreness in three cases and by stiffness in two cases. These cramps came on suddenly in the posterior crural muscles, sometimes while the patient was exercising, and were often severe enough to compel the patient to sink to the ground. The cramps were severe and painful, with a drawing sensation in the soleus, plantaris and gastrocnemius muscles. A few, whether intentionally or otherwise, have ascribed their misfortune to their occupation, and have tried to collect compensation.

Soreness in the calf muscles occurred alone in fifteen patients, was associated with stiffness in five cases and with cramps in three cases. This soreness most frequently came on after resting or on arising in the morning. All of these symptoms were moderately severe at first, increased in severity for twelve or eighteen hours, whereupon they subsided and in three days were gone altogether. Occasionally after three or four days, and more often at night a few shooting pains developed, starting in the feet and traveling up into the hips. These lasted only a few hours and then vanished.

Weakness of the feet and legs appeared in an average of three days after the onset in most cases. The patient first noticed that his feet were beginning to "flop" and that he had difficulty in raising the feet from the floor. This weakness began in the dorsiflexors of the foot, next involved the plantaflexors, then progressed to the leg and thigh. Most observers have mentioned only the footdrop in this disease. It is my opinion that plantaflexion was impaired almost simultaneously and equally with dorsiflexion. Plantaflexion of the foot is a more passive movement than dorsiflexion, therefore impairment of this function is not noticed by the patient and is less conspicuous to the observer. I have found on physical examination both functions equally impaired. For a few days (two to nine) the weakness of the lower extremities increased, and finally the patient found his feet almost useless. He continued to hobble around with some assistance for three or four days more, then gave up and went to bed. From this point on for several months there was exceedingly little change in the patient's condition.

Weakness of the hands is an interesting phenomenon because of the consistency with which it came on after an average period of ten days from the onset of the initial symptoms. The length of this period was also found to be ten days by Smith and Elvove,[10] while Bennett[1] found that this weak-

ness appeared in three days in one-half of his cases. The patient first noticed impairment of extension and flexion of the wrists and fingers. He soon was unable to button his clothes, remove his glasses, or to grasp objects with any degree of strength or precision.

Another interesting observation was made in regard to the order in which the extremities first become involved. Thirty-two patients stated that their right hand was first to weaken. In only four cases was the left hand first involved, and one of these patients was left handed. In the lower extremities the onset was about symmetrical. That the lower extremities were first affected can easily be explained by the fact that the longer neurons in the lower extremities are more susceptible to degeneration. However, the only explanation I can offer for the right hand being involved first is that the most used extremity is more prone to weakening.

Neurologic Findings

In many diseases of the nervous system the examination may be disposed of in favor of a good history. In Jamaica ginger paralysis, however, the histories are exceedingly variable in contrast to the striking similarity and consistency in the clinical findings. In most cases the condition could be diagnosed on the clinical findings alone. Two patients in the series applied for compensation for their illnesses. One said he had slipped and had fallen while carrying a load up an incline, following which he developed weakness, then paralysis. The other patient said he had been hit by a swinging beam. Both denied having taken Jamaica ginger, but had typical findings of this type of paralysis.

If the patient is only slightly disabled and is walking around, he will have a "high stepping" gait, lifting his knees high in order that the dropped feet may clear the floor. The more disabled patient is found lying with legs extended, feet "dropped" and hands lying almost useless at his side. When the arms are raised the wrists assume a typical wrist drop. The feet appear sallow, and are cold and damp. The use of the muscles of the feet is almost entirely lost. The power of the anterior, posterior and lateral crural muscles is more or less symmetrically lost (96 per cent). The anterior femoral muscles (quadriceps and sartorius) become powerless in about half of all cases. In the upper extremities both flexors and extensors of the wrists are lost in 38 per cent of the patients, while in an additional 14 per cent the extensors are more involved than are the flexors. Where the weakness in the hands is only slight, adduction and flexion of the thumbs are the only movements impaired.

Sensation was remarkably normal in nearly all cases in this series, a feature which helps to distinguish Jamaica ginger paralysis from other types of peripheral neuritis. This finding has been so constant that I have come to believe it typical of this type of neuritis, even in view of the fact that Wilson[3] and Goldfain[6] state that there is a loss of deep pain sensation in the lower extremities, and a loss of vibration sense below the knees. In many of these cases the vibration sense was acute in the toes, causing

the patient considerable distress when touched with the tuning fork. In all except five cases both exteroceptive and proprioceptive sensation was entirely normal. This clinical observation was substantiated pathologically by Vonderahe[7] who found only minor changes in the sensory columns and nuclei. Of the five patients who did have sensory changes, four had findings which strongly suggested that either syphilis or alcoholic neuritis was the cause of the impairment. (See table II).

presents no explanation for the proprioceptive loss.

Irregularity of pupils was found in 28 cases, and inequality of pupils was found in 13 cases. In only nine of these two groups of patients were there positive Wassermann reactions. The light reflex was definitely slow or absent as compared to the reaction to convergence (accommodation) in 50 per cent of the cases in this series. Only six of these had positive Wassermann tests and two more gave a history of having had syphilis, but had

TABLE II
History and Findings of Patients Showing Sensory Changes.

Case	History of Lues	Wass.	Pupil		Sensation	
			Contour	Light Reaction	Extero-ceptive	Proprio-ceptive
I	Yes	Neg.	Irreg.	Absent	Absent	Absent
II	No	Neg.	Reg.	Present	Present	Absent
III	Yes	Pos.	Irreg.	Fair	Absent	Present
IV	Yes	Pos.	Irreg.	Absent	Present	Absent
V	No	Pos.	Irreg.	Fair	Present	Absent

Case I had taken one and a half bottles of ginger a day for six months, was considered a "moderate" alcoholic, and had taken a small amount of liquor before taking the "Jake." He therefore had cause for a true alcoholic neuritis resulting in both extero- and proprioceptive loss.

Cases IV and V were obviously tabetic, which could explain the proprioceptive loss. Case III had syphilis, irregular pupils, a slow pupillary reaction to light, and had taken two bottles of ginger a day for three years. As loss of exteroceptive sensation without a loss of proprioceptive sensation is rather unusual in both Jamaica ginger neuritis and syphilis, this case was probably one of alcoholic neuritis. Case II is the only one which negative serology. The findings of pupillary changes in so many cases and in the absence of other disease, forces one to conclude that the same process affecting other nerves is also inhibiting the pupillary reflex.

Blurring of the nasal side of the disc margin was discovered in eleven patients. In two of these the discs were definitely "choked." Nielsen and Verity[11] observed Argyll-Robertson pupils and optic neuritis in a patient suffering with peripheral neuritis. On the other hand Harris[2] and Vonderahe[7] found no changes in the discs or cranial nerves in any of their patients. The temporal halves of the discs were pale in twelve patients in this series. In two of these patients the discs were definitely atrophic,

probably due to syphilis. One patient who had optic atrophy had been thoroughly intoxicated before taking his ten bottles of ginger, suffered moderately severe retrobulbar soreness, and had a positive Wassermann test with absent pupillary light reflexes.

In general, the deep and superficial reflexes are a fair indication of the extent of the degeneration in the peripheral nerves and anterior horn cells of the cord. The tendo Achillis reflex is the first to be lost, and was absent in all cases except one in which only the left was elicited and another in which both Achilles' reflexes were present and normal. I believe the absence of this reflex is a constant and reliable sign in this disease as in other types of peripheral neuritis, even though in Vonderahe's cases[7] the abdominal, Achilles' and patellar reflexes were all normal.

The cremasteric reflexes are next after the Achilles' reflex to be lost, being entirely absent in half of the cases and in nine more were lost on one side. In 21 cases in which the abdominal reflexes were entirely normal the cremaster reflexes were absent, or were absent on one side and considerably decreased on the other. Abdominal reflexes were completely absent in twelve cases, and in all but one of these the cremaster reflexes were also absent. This is to be regarded as a point of considerable significance, showing the level to which the degeneration has progressed.

The patellar reflexes were lost in eighteen cases. In only four cases were these reflexes increased, a marked contrast with the findings in Bennett's[1] cases of which one half had hyperactive reflexes. In this series the fact that in eight cases the abdominal reflexes were still present while the patellars were absent shows how sharply the height of the ascending degeneration can be estimated, since the abdominals are supplied by the eighth to the twelfth dorsal segments, while the patellars are supplied by the third and the fourth lumbar segments.

The biceps reflexes were lost in only five cases; in two of these all other reflexes were lost, and in three only the abdominal reflexes remained. Of all patients in the series, one alone had no involvement whatever of the hands. It is assumed that the biceps reflex, being less often involved than those coming from lower down the cord, further indicates the extent of the degeneration and that the extent of the damage to the nervous system can easily be estimated by a careful examination of the various deep and superficial reflexes.

Conclusions

1. The disease can be definitely diagnosed on the physical findings alone. The history is often unreliable and is relatively of little importance.
2. The flexors of the extremities are affected almost equally with the extensors.
3. Sensation is seldom affected.
4. The lesion in Jamaica ginger paralysis is more than a neuritis. Clinical and pathological findings indicate that the process is an ascending degeneration, the extent of which is proportional to the amount of the chemical absorbed from the intestinal tract, and is manifest clinically by changes in the motor power of the extremities,

TABLE I

TABLE I

Showing greater loss of motor power and reflexes after taking larger doses of Jamaica ginger.

No. of Cases	Total No. Bottles	Ave. No. Bottles	No. of days of Drinking	Per Cent of Patients With Lost Function									
				Lost Power					Lost Reflexes				
				Leg		Thigh	Wrist						
				Flexor	Extensor	Flexor	Flexor	Extensor	Biceps	K. J.	Achilles	Abd.	Cremaster
10	6 to 20	11.4	4.6	100	90	60	60	70	20	60	100	20	60
20	1 or 2	2.1	1.5	95	95	35	5	30	5	25	95	20	35

and in the various deep and superficial reflexes.

5. Although impairment of vision is not elicited subjectively, the disease frequently delays the pupillary light reflex, often produces irregularity of the pupils, and occasionally gives an optic neuritis.

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Reduction in the Incidence of Syphilis Possible

"IS syphilis in America on the increase or on the decline? Certainly we rarely see the rupioid and malignant types of syphilis that were formerly encountered. We believe that with education of the medical profession and with proper education of the laity as to the consequences of this disease that much good has and will continue to result. We would doubly emphasize the necessity of early diagnosis and of thorough treatment along with the more general and universal use of prophylaxis. With these forward steps and with compulsory examination of all applicants for marriage, syphilis in the next twenty-five to thirty years would truly take an enormous decline. Perhaps the day will actually come with syphilis, as with typhoid fever, that the disease will be so rare that the medical schools will have difficulty in getting material for teaching purposes. This millennium however is unfortunately not yet at hand."

—(Harold N. Cole, M.D.: Some observation on the treatment of syphilis, *Am. Jr. of Syphilis,* 1932, xvi, 21.)

Peripheral Vascular Diseases

Treatment with Acetyl-choline Hydrochloride*

By W. C. WATERS, M.D., *Atlanta, Georgia*

UNSATISFACTORY restoration of function so frequently follows surgical amputations for the gangrene of peripheral vascular diseases that interes[t] in the treatment of such disturbances has been revived. Samuels[1] views the gangrene in these conditions as a self-limiting process and recommends conservatism until so much tissue has been destroyed that nonfunction appears to be inevitable.

Among palliative measures which have proved beneficial may be mentioned postural exercises,[2] the use of Ringer's solution by duodenal tube and by hypodermoclysis,[3] and the intravenous administration of sodium citrate[4] and sodium iodide solution.[5]

In 1926, Brown[6] introduced the use of typhoid vaccine given intravenously to determine which cases were suitable for sympathetic ganglionectomy. He determined the "vasomotor index" after the temperature had been made to rise by the injection. This is calculated as follows: The difference between the rise in mouth temperature and the elevation in cutaneous temperature divided by the rise in the mouth temperature. An index of more than two indicates a large degree of vasospasm in the disease, which ganglionectomy may be expected to relieve.

Following Brown's investigations, Allen and Smithwick[7] gave small doses of the vaccine intravenously at spaced intervals to patients having far advanced vascular lesions in whom the operation was contra-indicated because of low vasomotor indices. They observed that reactions from injections were similar to those following periarterial sympathectomy; namely, relief of pain, elevation of the surface temperature, and improvement in the appearance of the local lesions. Of the twenty-five cases treated in this manner, eighteen were markedly benefited. The objection has been offered by Spurling[8] that the severe constitutional reaction following the injection in these patients who are already debilitated, is undesirable.

The drug, acetyl-choline hydrochloride, was first used clinically by Villaret and Justin-Besançon[9] in 1926 in a case of Raynaud's disease, in which the course of the disturbance was markedly alleviated. These investigators later described its action, the indication for its use and the methods of administration. It is a powerful vasodilator, this effect being produced by action on the arteries and arterioles. That the capillaries are not affected is

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proved by the absence of flushing of the face following its administration[10] while ophthalmoscopic examination shows dilatation of the central retinal artery to twice normal size.[11]

Acetyl-choline should be given subcutaneously or intramuscularly. Administered orally, it is without effect; while given intravenously, it is highly toxic and may prove fatal.[12] The dosage varies from 50 to 100 mg., repeated at twelve to twenty-four hour intervals. As improvement in the disturbance indicates, this may be reduced to once, twice or three times weekly. According to Villaret and Justin-Besançon,[10] no untoward reactions have followed two thousand personally administered injections and they report its action to be maintained with repeated use.

They, further, have demonstrated a return of normal color and relief of pain in the affected parts from the use

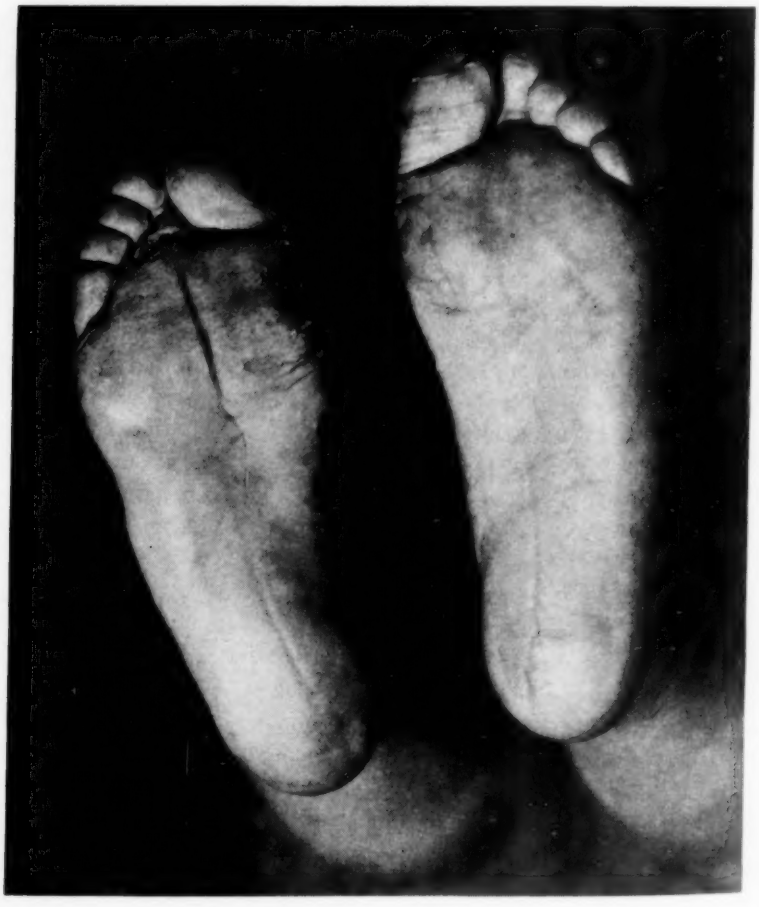

FIG. 1. Gangrene involving the large toe and medial surface of the foot. There is a trophic ulcer at the base of the second and third toes.

of acetyl-choline in Raynaud's disease; rest pain and intermittent claudication in thrombo-angiitis obliterans was relieved, and improvement of trophic lesions and an increase in the oscillometric index was obtained. They mentioned no effect on the peripheral temperature following its administration.

Since the volume of blood flow through an extremity is measured by the rate of heat elimination,[13] the estimation of the cutaneous temperature is of extreme importance in evaluating the effectiveness of treatment in peripheral disease. Diminution of surface temperature, particularly when associated with other signs of retarded blood flow, is characteristic of these disorders and as a rule improvement in the course of the disease is accompanied by elevation of the surface temperature in the affected parts.

In the cases herein reported, surface temperatures were taken after exposing the extremities to a room temperature of 70° F. for thirty minutes. Then, the bulb of a mercury thermometer was placed between the bases of the first and second toes which were strapped together with adhesive so that the skin was in contact with the entire surface of the bulb. Readings were made after the thermometer had been in place for three minutes. This method is accurate, simple and requires no expensive apparatus.

In one to three hours following the administration of acetyl-choline to these patients the cutaneous temperature was elevated from 2° to 5° C. The mouth temperature was not affected by the injection. This elevation lasted eighteen to twenty-four hours, at the end of which there occurred a drop to the original level. Accompanying this reaction the patients experienced a sense of warmth and relief of pain in the affected extremities. The administration of the drug daily, or every other day, over a period of time produced an increase of the surface temperature to a constantly higher level, complete relief of pain and eventually disappearance of the gangrene. Since the surface temperature of an extremity is an index to the

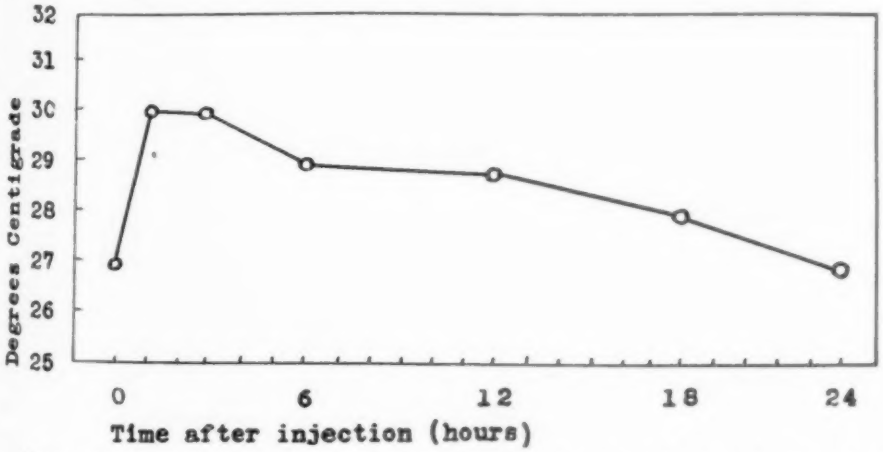

CHART 1. Surface temperature readings in case I after the injection of 100 mg. of acetyl-choline.

adequacy of its blood supply, a reduction in this reading after acetyl-choline has been discontinued should be accepted as an indication that the drug is still required.

The disadvantages of foreign protein administration are not encountered with the use of acetyl-choline. These are (1) the lack of a uniform and constant effect, (2) the possibility of vascular occlusion during the chill, (3) the necessity for hospitalization, and (4) the undesirability of the induction of fever for debilitated patients.

The following cases are selected to illustrate the immediate rise of the peripheral temperature following an injection of acetyl-choline to those having trophic lesions resulting from obliterative vascular diseases and to demonstrate the effectiveness of the use of the drug in the treatment of these disorders.

Case Reports

Case I. A woman, aged 46 years, was referred for treatment because of diabetic iritis. In addition to polyuria, excessive thirst and voracious appetite, she complained of pain in the feet radiating into the calves of the legs. Since there was diminution of all types of sensation in the legs, and pul-

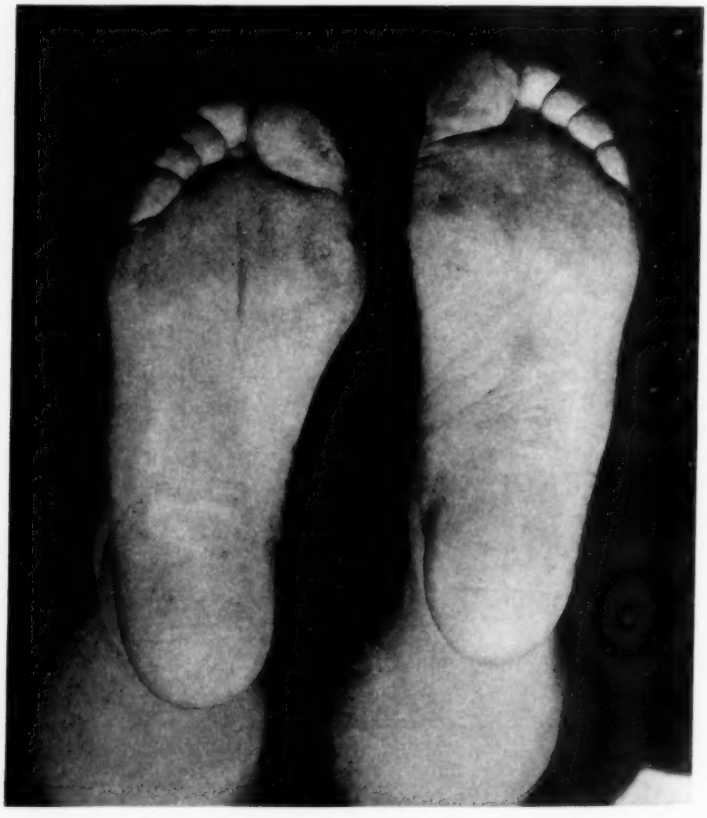

Fig. 2. Healing of gangrene and the ulcer three months later following the use of acetyl-choline.

sations in the dorsalis pedis and anterior tibial arteries appeared adequate, it was thought at the time that the pain complained of was due to diabetic neuritis.

Physical examination disclosed no abnormalities. The fasting blood sugar estimate was 250 mg. per 100 c.c. and the urine contained a large amount of sugar.

Following restriction of diet and the administration of 20 units of insulin daily, the urinary sugar disappeared and the fasting blood sugar returned to a normal level.

Nevertheless, two months later she developed an ulcerative lesion at the base of the first toe of the right foot. Shortly thereafter, gangrenous areas appeared at the bases of the second and third toes and over the plantar surface of the large toe (figure 1). In spite of the presence of apparently normal pulsations in the peripheral arteries, there was blanching of the feet with elevation and rubor with dependency. The surface temperature of the right foot was 27° and of the left 28° C.

In spite of rest in bed and the use of local heat, the gangrene appeared unimproved at the end of two weeks. One hour following the intramuscular injection of 100 mg. of acetyl-choline the cutaneous temperature in the feet was increased to 30° C. This elevation lasted twelve hours, at the end of which the temperature gradually dropped to the previous level (chart 1). The administration of the drug daily during the next two weeks resulted in marked improvement in the local lesions. A continuation of the injections twice weekly for the next three months produced complete healing of ulcerations (figure 2), disappearance of postural color changes and elevation of the surface temperature to a level constantly above 29° C. (chart 2).

Case II. A woman, 38 years of age, complained of small painful ulcerative lesions symmetrically distributed over the tips of the first, second and third toes of the feet. These had appeared five days previously. For years she had suffered with cold feet, more pronounced in the winter.

Digital examination revealed normal pulsations in the popliteal arteries but none were felt in the dorsalis pedis and anterior tibial vessels. The cutaneous temperature of the feet was 24° C. and postural color changes were marked.

The gangrene persisted in spite of the use of heat and rest in bed for a week.

One and one-half hours after the intramuscular administration of 100 mg. of acetyl-choline, the surface temperature of the feet increased to 29° C. (chart 3), and pulsations returned in the peripheral arteries. This reaction lasted for eighteen hours. The use of the drug in this dosage every other

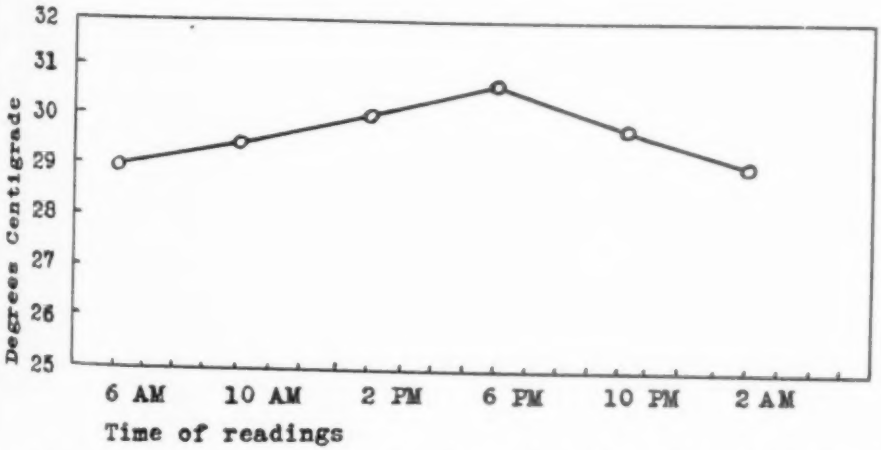

CHART 2. Surface temperature readings in case I showing a higher level after the gangrene had been healed by the use of acetyl-choline.

day for one month resulted in healing of the gangrene and the return of arterial pulsations in the feet.

Treatment was discontinued for the following two months, at the end of which time examination disclosed no signs of the previous vascular disturbance.

Case III. A man, 84 years of age, had complained of pain in the right leg on exercise for three years. Lately this had become steadily worse. Two weeks before the present observation he was seized with severe pain in the member which lasted twenty-four hours. This was evidently due to an acute arterial occlusion since he noticed bluish discoloration of the toes for the first time. Following this attack he suffered with constant pain in the leg which interfered with sleep.

Palpation showed absence of pulsations in the popliteal, dorsalis pedis and anterior tibial vessels of both sides while rubor with dependency and blanching with elevation of the right foot was marked. The skin over the weight bearing areas of the right foot was thickened and there was a small ulcer both on the lateral surface and on the heel.

The surface temperature of the right foot was 25° and of the left 26° C. One hour after the intramuscular administration of 100 mg. of acetyl-choline the surface temperatures were 28°. There was a gradual drop to the previous level at the end of twenty-four hours (chart 4). Marked amelioration of rest pain was obtained by the use of the drug given every other day for the next two weeks. Its continuation twice weekly during the following two months produced marked improvement in the trophic changes and complete cessation of pain. The peripheral vessels remained pulseless.

Summary

Three patients having trophic lesions due to vascular disease of the extremities were treated by intramuscular injections of acetyl-choline hydrochloride. Healing of gangrenous areas, relief of pain and elevation of the surface temperature to a higher level was obtained by the use of the drug. In one case pulsations in the peripheral arteries were re-established.

In one to three hours following an injection the cutaneous temperature in the affected parts was increased 2° to 5° C. This elevation lasted eighteen to twenty-four hours and was accompanied by a sense of warmth and relief of pain in the extremities.

The advantages of the use of acetyl-choline are (1) the ease of its admin-

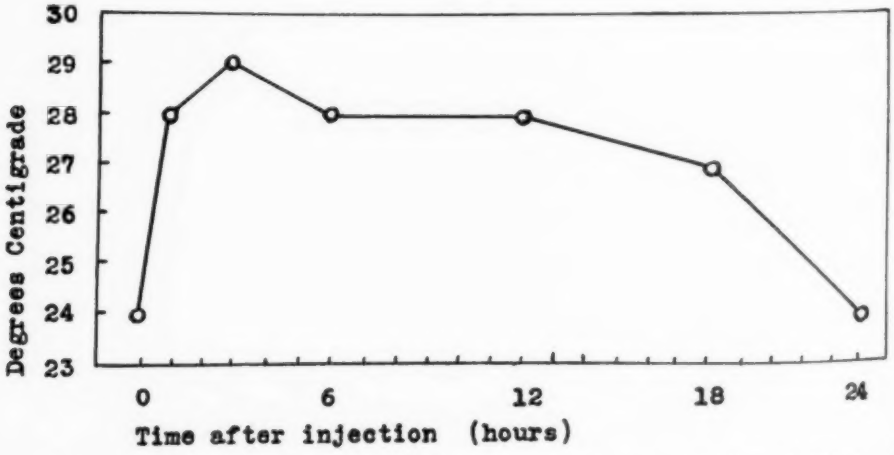

Chart 3. Surface temperature readings in case II after the injection of 100 mg. of acetyl-choline.

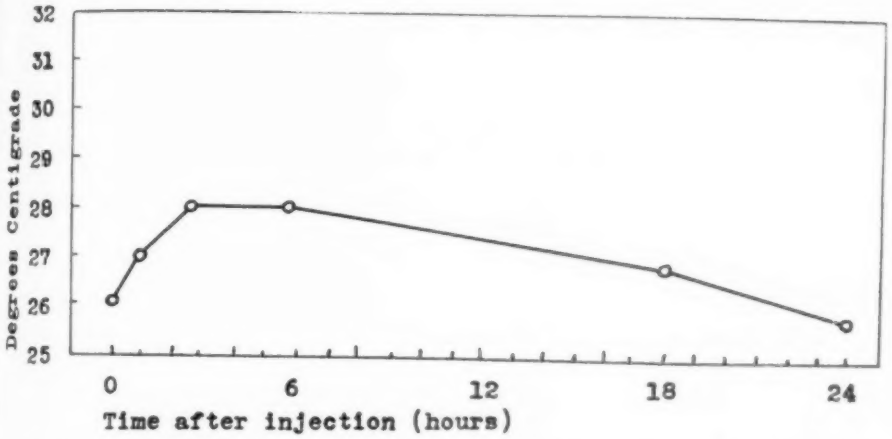

CHART 4. Surface temperature readings in case III after the injection of 100 mg. of acetyl-choline.

istration, (2) the absence of constitutional reactions following its use, and (3) the ability to maintain a constant and uniform elevation of the surface temperature by frequently repeated injections.

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Metastatic Malignant Tumors of the Brain*†

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IN THE diagnosis and treatment of tumors of the brain, one is always confronted by the possibility of any given tumor being secondary to some primary malignant tumor situated outside of the central nervous system. Many difficulties, however, are encountered in attempting to prove the metastatic origin of such a tumor. In the hope of gaining some knowledge which would aid in clinical recognition of the true nature of these lesions, a clinical, statistical, and pathologic survey of the material available at The Mayo Clinic was undertaken.

Ninety-five patients examined in The Mayo Clinic in the ten years ending January 1, 1929, were given a diagnosis of metastatic malignant tumor of the brain. This series of cases, for purposes of study, has been divided into three groups. Group 1 consisted of twenty-three cases in which complete necropsy, including examination of the brain, was performed. In each of these cases diagnosis was first made from gross appearance of the tumor; a primary malignant tumor outside of the central nervous system was found in each case, and at least one secondary malignant tumor was found within the brain. These diagnoses all were confirmed by microscopic examination. Group 2 consisted of forty-four cases in which there was a clinical picture of tumor of the brain but in which there was no gross or microscopic examination, of any kind, of brain tissue. However, the presence of a primary malignant tumor outside of the central nervous system was confirmed in each case by necropsy, by biopsy, or by operation at a time previous to the appearance of symptoms of tumor of the brain. This confirmatory examination included, in all cases, microscopic studies. Group 3 consisted of twenty-eight cases in which there was a clinical picture of tumor of the brain and also a clinical picture of primary malignant tumor outside of the central nervous system. In this group gross or microscopic examination of tissue was not made at the clinic. However, some of the patients previously had been operated on elsewhere, at which time a diagnosis of malignant tumor outside of the central nervous system had been made. These diagnoses in some instances had been substantiated by microscopic studies. Detailed neurologic studies were conducted in eleven cases of group 1 and in seventy-seven cases of the entire series.

In none of the ninety-five cases was there metastasis to the skull without evidence of intracranial involvement

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†From the Division of Medicine, The Mayo Clinic.

and in none was the intracranial involvement by direct extension, such as occurs in cases of tumor of the nasopharynx, accessory nasal sinuses, orbits, or eyes.

The diagnoses of the primary and secondary tumors of group 1 were made by the Section on Pathologic Anatomy of The Mayo Clinic. Emphasis in this study was placed on the reaction of the tissue of the brain to the presence of the tumor, rather than on study of the nature of the tumor. The first eleven cases of group 1 were selected for special pathologic study. Sections for microscopic examination were taken from several regions: from the juncture of the tumor and the adjacent tissue of the brain, from the surface of the cortex at points distant from the tumor, and from the choroid plexus. Stains used in each instance were hematoxylin and eosin, iron hematoxylin, Scharlach R, toluidine blue, van Gieson's and Mann's.

Analysis of Material

The cases comprising groups 2 and 3, in which the malignancy of the cerebral lesion had not been authentically determined, although the clinical picture was that of a primary malignant tumor outside of the central nervous system and a secondary tumor within the brain, have been subjected to clinical and statistical analysis. The results of the survey of the cases of group 1 are compared to a similar survey of the larger series of cases comprising groups 2 and 3.

Clinical Studies. The average age of the patients of the entire series of ninety-five cases was 47.5 years. There were only twelve patients who were less than thirty-five years of age, of whom three were children who probably were suffering from primary tumors of the suprarenal gland. Thus, the average age of the patients falls within the accepted cancer age. In spite of the high incidence of metastasis to the brain from carcinoma of the breast, which would tend to increase the number of cases among women, cases were about evenly divided between the sexes. There were forty-nine males and forty-six females. There was an average loss of weight of 24 pounds in thirty-four cases in which the weight of the patients had been accurately recorded.

An attempt was made in those cases in which the primary lesion should have been readily recognized, as in cases of carcinoma of the breast and in those cases in which the onset of symptoms referable to the primary lesion could be fairly accurately determined, to estimate the duration of existence of the primary lesion prior to the onset of cerebral symptoms. The average thus obtained was twenty-one months for the cases of group 1, and 31.5 months for the cases of each of the other groups. The longest interval between the onset of symptoms of the primary lesion and of those of the cerebral lesion in a case of group 1 was 6.5 years; the primary tumor was a hypernephroma. The corresponding interval in a case of group 2 was nine years; the primary tumor was a carcinoma of the carotid body. The interval in a case of group 3 was twelve years; the primary tumor was a carcinoma of the breast.

The onset of cerebral symptoms had antedated the patient's visit to the clinic for an average of three months

for the cases of group 1, and for 4.5 months for the cases of each of the other groups.

The average length of life from the time of examination at the clinic, until death, was 3.5 months, and the time from onset of cerebral symptoms until death was eight months in those cases of groups 2 and 3 in which the time of death had been reported.

The presenting symptoms in the entire group of ninety-five cases were directly referable to the cerebral lesion in sixty-eight and to the primary lesion in only fifteen. There were symptoms referable to both the primary and the cerebral lesion in twelve of the cases. In seven cases of group 1 in which the patients presented themselves at the clinic because of cerebral symptoms, mention was not made of symptoms referable to the primary lesion. Cerebral symptoms were merely a terminal feature in twelve cases of group 1.

The symptoms referable to the cerebral lesion most frequently complained of were headache, vomiting that often was of a projectile nature, disturbances of vision and of speech, vertigo, and transient aphasia. Headache was the predominant complaint. The clinical signs most frequently noted were monoplegic or hemiplegic paresis, cranial nerve palsy, ataxia, and jacksonian seizures.

The frequent incidence of mental disturbance is very striking in all three groups. In study of mental disturbance, only those cases were used which had been observed by the Section on Neurology of The Mayo Clinic. Definite mental changes were observed in 75 per cent of the cases of group 1, in 45 per cent of the cases of group 2, and in 56.5 per cent of the cases of group 3; the incidence for the entire series was 57 per cent. The mental disturbance varied from mental sluggishness, to confusion and even to stupor in the more advanced cases. Emotional disturbances of varying degree and duration were present in a smaller percentage of cases.

Of the eighty-four cases of the entire ninety-five in which the ocular fundi had been examined, choked disk was recorded in 40 per cent. Likewise, in 41 per cent of those cases of group 1 in which the fundi had been examined there was choked disk. Optic atrophy and hemianopsia were present in a smaller percentage of cases of the entire group. There were nine cases in which there were perimetric visual field defects and three cases in which optic atrophy was present.

Study of the clinical localization of the cerebral tumors failed to disclose any region of predilection for the development of metastasis in the brain (table 1). The sixteen cases of group 1, in which detailed neurologic studies had been conducted, and in which necropsy, including examination of the

TABLE 1

Clinical Situation of Tumor of the Brain of the Seventy-seven* Patients Who Underwent Neurologic Examination.

	Groups			
Situation	1	2	3	Total
Right side of cerebrum	2	11	6	19
Left side of cerebrum	2	9	4	15
Chiasma			1	1
Cranial nerves		3	3	6
Brain stem	1	3	2	6
Cerebellum	1	5		6
Base		2		2
Gasserian ganglion		1		1
Third ventricle		2		2
Meninges	1			1
Not stated	9	9	6	24

*Diagnosis was of involvement of more than one region in some cases.

brain, had been performed, were the only cases in which clinical diagnosis and localization could be checked accurately against pathologic changes. The situation of the cerebral lesion was correctly diagnosed in seven of the sixteen cases. In the remaining cases of the sixteen either localizing signs were absent or dissemination of the signs led to incorrect diagnosis of an inflammatory lesion.

A clinical diagnosis of metastatic malignant tumor of the brain was made in six of the sixteen cases. In these six cases there was an obvious primary malignant tumor elsewhere than in the brain, recognizable metastasis, or a history of previous operation for a malignant tumor situated outside of the central nervous system.

A diagnosis of primary tumor of the brain had been made in five of the sixteen cases, none of which presented either symptoms or signs referable to a primary lesion elsewhere. However, the primary lesion proved to be carcinoma of the lung in three cases and carcinoma of the kidney in two cases.

In the preceding two paragraphs, eleven of a particular group of sixteen cases have been considered. In the remaining five of these sixteen cases the dissemination of signs, the paucity of localizing signs, and failure to recognize or sufficiently to consider the primary lesions led to the assumption that the cerebral manifestations were on the basis of inflammatory diseases. In one of these five cases in which a clinical diagnosis of tuberculosis of the lung, spine and brain had been made, necropsy disclosed a primary carcinoma of the lung with metastasis to four vertebrae, situated partly in the thoracic and partly in the lumbar region, to the subjacent meninges in the thoracic region, and to the brain. In the second of the five cases, in which a diagnosis of syphilis of the central nervous system had been made, necropsy disclosed a primary carcinoma of the lung, with metastasis to the meninges covering the midbrain and cerebellum, and healed pulmonary tuberculosis. In the third of the five cases, in which the clinical diagnosis was infectious meningo-encephalitis, secondary to the toxemia of pregnancy of seven months, necropsy revealed multiple, bilateral metastatic nodules in the cerebrum and cerebellum, secondary to carcinoma of the breast, for which operation had been performed three years previously. In the fourth of the five cases, in which a clinical diagnosis of recurrent carcinoma of the sigmoid had been made, and in which at necropsy a metastatic nodule had been found in the cerebellum, a clinical diagnosis of general paralysis of the insane had been made in view of an old history of syphilis, rapidly developing and marked mental deterioration, and the presence of clinical signs considered characteristic of syphilis of the nervous system. The fifth patient of these five, who was brought to the hospital in a moribund state, was found at necropsy to have a primary carcinoma of the pancreas, with generalized carcinomatosis and multiple cerebral metastatic growths.

There were five cases in group I in which there was carcinomatous involvement of the meninges. Two cases in which the primary lesion was an asymptomatic carcinoma of the lung have been considered in the preceding paragraph. In a third case, one of car-

cinoma of the stomach presenting terminal cerebral manifestations, a clinical diagnosis of carcinomatous meningitis secondary to gastric carcinoma was made prior to death, and this diagnosis was substantiated at necropsy by demonstrating carcinomatous invasion of the pia-arachnoid. In a fourth case, one of carcinoma of the breast in which cerebral symptoms were terminal, but in which neurologic studies had not been conducted, necropsy disclosed carcinomatous invasion of both the dura and pia-arachnoid. A clinical diagnosis of inoperable carcinoma of the breast, with metastasis to the midbrain, was made in a fifth case, in which necropsy disclosed several regions of metastasis to the cerebral cortex; there was also metastasis to the substance of the left third cranial nerve and to the pia-arachnoid covering the midbrain with extension of the tumor cells along the pial prolongations into the subjacent brain.

Laboratory Studies. There was a slight to a moderate degree of anemia in 28 per cent of eighty-eight cases in which blood counts had been made. Of eighty cases in which Wassermann tests of the blood had been made, a positive reaction occurred in only one instance.

Examination of spinal fluid had been conducted in twenty-two cases. Among these twenty-two there was one instance in which the Wassermann test of the spinal fluid was positive, but in this instance the Wassermann test of the blood was negative. Yellow spinal fluid was obtained in six cases, three of which belong in group 1, and in which, at necropsy, involvement of the ventricle or meninges by metastatic lesion was found. There were not more than eleven cells for each cubic millimeter of spinal fluid in any case.

Roentgenologic methods failed to reveal the presence of many of the growths encountered. The entire experience was as follows: Roentgenograms of the thorax had been made in seventy-eight cases, in 47.5 per cent of which there was evidence of pathologic change. A diagnosis of primary or metastatic malignant growth of the lung was correctly made in 37 per cent of the cases. Of the fourteen cases of group 1 in which roentgenograms of the thorax had been made and in which at necropsy pulmonary metastasis had been demonstrated, evidence of pathologic change in the roentgenogram was reported in eight cases (51 per cent). However, the incorrect diagnosis of inflammatory lesion had been made in four of the eight cases.

Metastasis or other pathologic changes had been reported in 21 per cent of the sixty-three cases in which roentgenograms of the head had been made.

Pathologic Studies. The lung, breast and kidney were the sites of the primary lesion in fifty-one of the ninety-five cases, an incidence of 58.6 per cent of those cases in which the site of the primary growth could be determined. Thirteen of these fifty-one cases were in group 1; that is, 56.6 per cent of the cases comprising group 1 (table 2).

It will be recalled that the nature of the primary lesion, outside of the central nervous system, was determined by microscopic studies in all cases of groups 1 and 2. The cases in which the diagnosis was carcinoma, hypernephroma or melano-epithelioma were classed together as cases of carcinoma.

TABLE 2
Situation of the Primary Malignant Tumors in all Cases Studied.

Situation	Groups 1	2	3	Total
Breast	5	20	3	12
Kidney	3	4	5	12
Lung	5	1	3	9
Skin	2	3		5
Suprarenal gland	2		3	5
Colon	2	1	1	4
Thyroid gland	1	1	2	4
Stomach	1	1	1	3
Testis		2	1	3
Bone		2	1	3
Esophagus			1	1
Pancreas	1			1
Gallbladder		1		1
Prostate gland			1	1
Uterus		1		1
Tonsil		1		1
Parotid gland		1		1
Carotid body		1		1
Eye		1		1
Undetermined	1	3	4	8

whereas the cases in which the diagnosis was sarcoma, lymphosarcoma, and Hodgkin's disease were classed together as cases of sarcoma. In fifty-nine cases the growths were classified as carcinomas, an incidence of 88 per cent of the cases comprising groups 1 and 2. Six cases in which the growths were classified as sarcomas and one case each in which they were classified as myeloma and as neuroblastoma accounted for the remaining 12 per cent of the cases.

In general, metastasis was widespread throughout the body. Pulmonary involvement, either primary or secondary, was proved in nineteen of the twenty-three cases which composed group 1, an incidence of 82.6 per cent of the cases. There were five cases of primary carcinoma of the lung and fourteen cases of metastasis to the lung. This leaves four cases of group 1 to be accounted for. Two of these, in which metastasis to the lung did not occur, were cases of carcinomatous meningitis in which the brain tissue proper was not invaded. Of the two remaining cases, one was a case of sarcoma which had metastasized throughout the body in the fat-bearing tissues, and the other was a case of melanoepitheliomatosis.

In the cases of group 1, in which metastasis occurred to the tissue of the brain, secondary nodules were found to be scattered irregularly throughout the gray and the white matter; just as in clinical examination, so in this examination, no site of predilection for the development of metastasis was noted. The tumors were usually rather sharply demarcated from the adjacent brain tissue and often were the site of rather marked necrosis and hemorrhage. Metastasis was single in seven cases and multiple in thirteen. It seems appropriate here to call attention to the case in which more than thirty metastatic nodules were counted. In the remaining three cases the involvement was confined primarily to the pia-arachnoid (figure 1).

Microscopic examination in most instances confirmed the impression that masses were rather sharply demarcated from the adjacent tissue, but in only two cases was a definite fibrous capsule present (figures 2 and 3). The tumors were usually decidedly vascular, and there was hemorrhage into the tumor. The tumors in some instances were composed of solid masses of tumor cells undergoing various stages of degeneration, whereas in other instances the tumor cells occurred singly, or as islets of tumor cells in a well-preserved state. The amount of reaction in the tissue of the brain adjacent to the tumor appeared to vary with the size and type of the tumor; it was less in the small tumors and in the two

FIG. 1 Case 10. Small pearly white metastatic nodules scattered over inner surface of dura.

FIG. 2. Case 1. The zone of demarcation, with a fibrous capsule, dividing the brain below from the tumor focus above. Rarefied appearance and swollen astrocytes in the subjacent brain tissue (x 75).

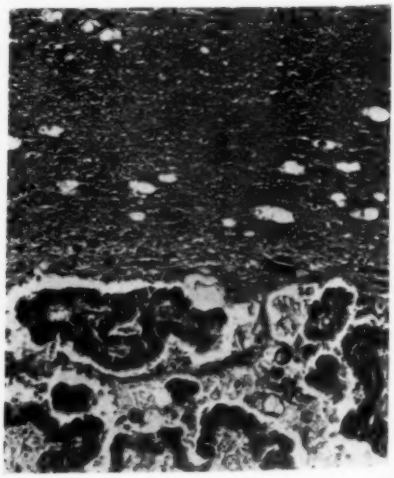

FIG. 3. Case 3. Demarcation zone dividing the brain tissue from the tumor focus, without a capsule of connective tissue. Rarefaction and mild glial proliferation (x 75).

cases of melano-epithelioma, as compared to the cases of carcinoma. This zone frequently presented a rarefied or sieve-like appearance (figures 4 and 5). The number and size of the blood vessels were usually increased, and frequently they formed the center of an outlying focus of tumor cells. Frequently tumor cells and scavenger cells could be demonstrated adjacent to and in the perivascular spaces of blood vessels in this zone. There was astrocytic proliferation, and in case of involvement of the gray matter, marked destruction of the ganglion cells. In the brain tissue distant from the tumor there were usually only slight changes. This zone occasionally appeared rarefied. There was usually proliferation of the astrocytes, and occasional gitter cells. Satellitosis was commonly observed in the cortex. In two cases the choroid plexus was invaded by tumor cells. There was no invasion of the meninges secondary to invasion of the tissue of the brain, except when the tumor came into direct contact with the surface of the brain. There was an occasional inflammatory reaction in the meninges, as evidenced by increased vascularity and the presence of lymphocytes, polymorphonuclear leukocytes, plasma cells, and erythrocytes, especially if the tumor was in close proximity to the surface of the brain.

In cases of carcinomatous meningitis the subarachnoid space was distended with tumor cells existing singly or as masses (figure 6). There was a moderate amount of proliferation of connective tissue. Lymphocytes, polymorphonuclear leukocytes, plasma cells and erythrocytes were found interspersed between the tumor cells. In some sections the tumor cells were found extending along pial prolongations into the sulci and invading the subjacent cortex (figures 7 and 8). There was little reaction in the tissue of the brain except for mild, generalized glial proliferation.

Comment and Comparison of This Series with Observations and Opinions in the Literature

The literature dealing with secondary carcinoma and sarcoma of the brain has been ably reviewed by Kaufmann, Gallavardin and Varay, Maass, Lilienfeld and Benda, Heinemann, Beerman, Humbert and Alexieff, Walshe, Lissauer, Schwarz and Bertels, Meyer and Grant.

Krasting gave the ratio of 1:3 as the incidence of metastatic to primary tumors of the brain at the Basel Hospital for a period of thirty-five years. This figure, obtained from the postmortem service of a large general hospital, does not hold for the clinical incidence in a large diagnostic center. Sixty-one cases of metastatic tumor of the brain and 1,308 cases of primary tumor of the brain were seen at The Mayo Clinic from 1919 to 1925 inclusive, giving a ratio of 1:20 for secondary to primary tumors of the brain. This figure is in close agreement with that of Grant, who reported an incidence of 4 per cent for secondary as compared to primary tumor of the brain from the Peter Bent Brigham Hospital.

Krasting, in a review of 12,730 postmortem examinations performed at the Basel Hospital from 1870 to 1905, reported 1,078 cases of carcinoma, in 817 of which the brain had been examined, and 160 cases of sarcoma,

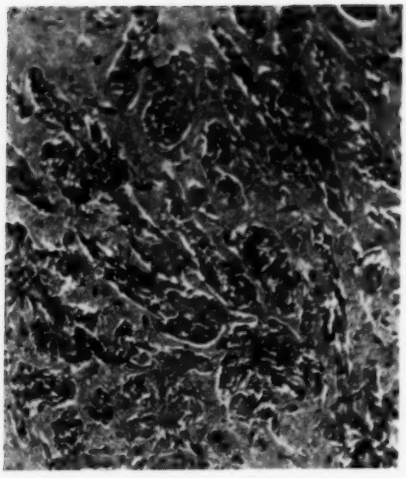

FIG. 4. Case 11. Islets of tumor cells extending into the adjacent brain with intervening brain tissue forming the so-called transition zone (x 75).

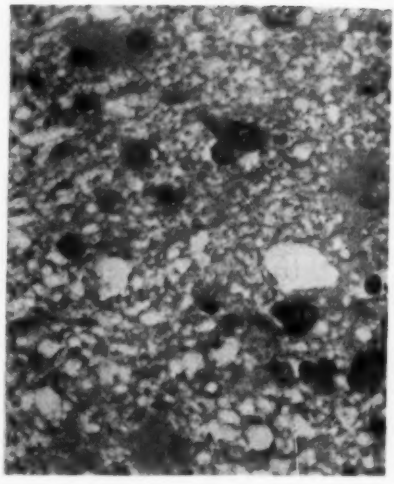

FIG. 5. Case 1. Brain tissue adjacent to the tumor. Rarefaction and formation of gemastite glial cells (x 350).

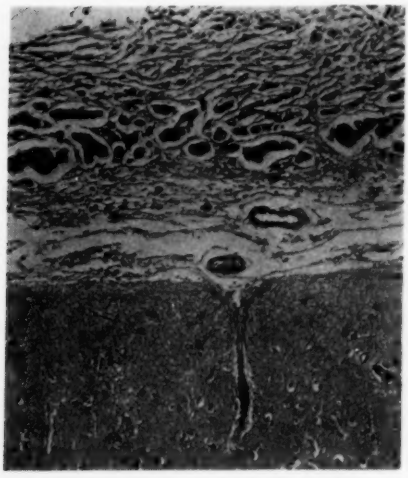

FIG. 6. Case 10. Carcinomatous meningitis; tumor cells occur either singly or as masses. The subjacent cortex is represented, and there is a blood vessel running in from the surface. Neither the perivascular space, nor the tissue of the brain proper is involved by the tumor cells (x 75).

FIG. 7. Case 6. Extensive involvement of the pia-arachnoid in a case of carcinomatous meningitis with extension of the tumor cells along the pial prolongations and involvement of the adjacent cerebellar tissue (x 75).

in 118 of which the brain had been examined. The incidence of metastasis, in those cases in which the brain was examined, was 5.7 per cent for the group with carcinoma and 11.6 per cent for the group with sarcoma. Gallavardin and Varay placed the incidence of metastasis to the brain as once in every seventeen to eighteen cases of malignant tumor.

Metastasis in general is widespread throughout the body in those cases in which there is cerebral metastasis. The lung was involved, either primarily or secondarily in 83 per cent of those cases in this series in which necropsy was performed. This tends to substantiate Kaufmann's view that pulmonary metastasis enhances cerebral metastasis.

Metastatic growths in the brain, in those cases in which authors have given their number, usually have been multiple and diffusely scattered. Metastatic growths in the tissue of the brain were multiple in 65 per cent of my series and in 66 per cent of Globus and Selinsky's series.

The incidence of localization of the metastatic growths in various parts of the brain appears to vary with the authors' individual experience. My series discloses no especial site of localization for the metastatic growths. Gallavardin and Varay found the largest proportion of metastatic growths in the cerebrum. Ewing, in writing of carcinoma of the breast, stated that they may metastasize to any part of the brain but are especially likely to metastasize to the cerebellum. Spiller and Weisenberg found involvement of the central convolutions, the cerebellum, and the temporal lobes in order of frequency in which they are named. It is generally agreed that the tissue of the brain is more often involved than the meninges. Cranial nerves are occasionally involved, either directly through metastasis to the substance of the nerve, or indirectly at their point of emergence from the meninges, when the latter are invaded by the tumor cells.

There is considerable variation of opinion as to the amount of reaction which the presence of the tumor excites in the surrounding tissue of the brain. Fried expressed the belief that there is no reaction, that the tissue of the brain merely melts away before the advance of the tumor. Buchholz, Kölpin, and Gallavardin and Varay stated that the tissue of the brain is merely pushed aside by the advance of the tumor, without actually being destroyed and without provoking reactive phenomena. Heinemann, Conighi, Morse and Fischer have reported on this aspect of the subject. Hassin and Singer re-

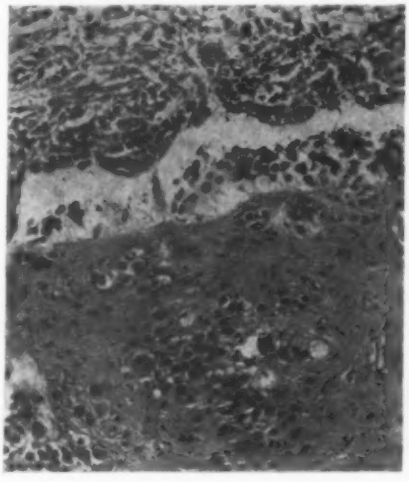

FIG. 8. Case 5. Extensive neoplastic invasion of the pia-arachnoid over the midbrain with small foci of tumor cells penetrating the subjacent cortex (x 75).

ported focal (masses) and diffuse (encephalitic) lesions in cases of secondary carcinoma involving the tissue of the brain. They expressed the belief that there are generalized reactive phenomena characterized by the formation of new capillaries and proliferation of glial cells, and that there are degenerative changes in the ganglion cells most marked in the tissue of the brain adjacent to the tumor. In the pia-arachnoid and the choroid plexus dilated vessels were constantly present, and there were lymphocytes and gitter cells. In carcinoma of the meninges, the only pathologic element found outside the tumor cells was the presence of gitter cells, plasma cells, and macrophages in the pia-archnoid, and some proliferation of glial cells in the subjacent cortical tissue.

In the eleven cases of group 1 (paragraph 5) in this series in which detailed microscopic studies were made of sections taken from the tumor, of the adjacent tissue of the brain and of tissue of the brain distant from the tumor, the pathologic changes were essentially in agreement with those of Hassin and Singer.

The incidence of metastasis to the brain varies considerably with the situation and nature of the primary tumor. The general consensus of opinion appears to be that a primary carcinoma which gives rise to secondary tumor of the brain is most likely to be in the lung or breast, and that a primary sarcoma which gives rise to secondary growth in the brain is most likely to be in the skin or lymph nodes. Ewing and Krasting expressed the belief that melanotic tumors of the skin are especially prone to metastasize to the brain.

Maass, in a study of carcinomatous meningitis, found the stomach, lungs, and breast to be the site of the primary tumor in the order in which they are named. Fried, in a study of nineteen cases of primary carcinoma of the lung in which necropsy was performed, found cerebral metastasis in nine of eleven cases in which the brain was removed. He expressed the belief that the greater incidence of metastasis to the brain from primary malignant tumor of the lung, as compared to malignant tumors of other organs, is due to the fact that the lung acts as a filter in case of metastasis from other organs, whereas there is no natural barrier between the brain and the lung. Krasting, in a review of 130 cases of cerebral metastasis, found the primary lesion in the breast in forty cases, and in the lung in twenty-nine cases, an incidence for these two organs of 50 per cent of the entire series. I find, by including the kidney along with the lung and breast, that metastasis to the brain arose from one of these three organs in 56 per cent of Krasting's series, in 51 per cent of Grant's series, in 56.5 per cent of my series, and in 54 per cent of ninety-four cases in which the situation of the primary tumor was stated, among 108 cases which I reviewed indiscriminately from the literature.

Little difficulty should be encountered in recognizing the primary tumor when it is in the breast. Tumors in the lung and kidney, however, are prone to run an asymptomatic course. At other times, the cerebral manifestations so overshadow any symptoms which may be referable to the primary lesion that the true nature of the malady is not recognized. Fried stated

that in cases of primary carcinoma of the lung there may be symptoms referable to the thorax, the condition may run a silent course, or there may be symptoms referable to the metastases only. He expressed the belief that the clinical features are amazingly scant as compared to the amount of tissue involved and the grave nature of the lesion. His opinion was that metastasis to the brain occurs early, often masking the clinical picture of the primary lesion. In his series of cases of primary carcinoma of the lung, five patients presented symptoms due to the cerebral metastasis; the primary pulmonary lesion was discovered only accidentally following operation on the brain or at necropsy. Seven of the eight cases in my series of proved primary carcinoma of the kidney or lung with metastasis to the brain, were accompanied neither by symptoms, nor, with one exception, by clinical signs referable to the primary lesion.

Silent primary tumors, and foci of metastasis may exist in other organs, as illustrated in a case of group 3 in which a primary carcinoma of the prostate gland had metastasized to the lungs, spine and brain without symptoms referable to any lesion except the cerebral one. Cerebral symptoms had been noted for an average period of three to four months prior to the time of examination. Grant reported an average interval of four months between the onset of cerebral symptoms and the time of examination.

Choked disks occurred in 40 per cent of the cases. This is practically the same incidence of occurrence as in primary tumor of the brain. Likewise, the degree of choking varies as much as in primary tumors of the brain. In my study the cerebral symptoms and signs were frequently of a bizarre and disseminate nature, varying in intensity from day to day. In cases of multiple metastasis, a single lesion situated in a vital center may give origin to the cerebral symptoms and signs noted; the other lesions may be in silent regions. Globus and Selinsky stated that multiplicity of lesions will, in the majority of cases, lead to dissemination of objective signs.

Mental disturbance appears to be one of the outstanding features in metastatic tumors of the brain. The mental symptoms associated with metastatic tumor of the brain appear to be more marked than those associated with primary tumor of the brain. The presence and severity of mental symptoms appeared to bear possible relationship to the presence and severity of the encephalitic changes in all cases except one. Lewis reported a case in which there had been a sudden onset of psychic manifestations diagnosed by several eminent psychiatrists as a catatonic type of dementia precox; on the later development of neurologic signs, the diagnosis had been changed to encephalitis, and it was not until necropsy that it was learned that the symptoms were due to cerebral metastasis from a primary malignant growth, probably in the lung. Mental symptoms occurring with metastatic tumor of the brain may be readily confused with those occurring in the ordinary type of psychosis. The similarity of such symptoms to those of general paralysis of the insane has been reported by Smith, Siefert, Elzholz, and von Heyde and Curschmann. Van Hasselt reported a case in which the diagnosis was senile dementia.

Maass reported a case presenting acute psychosis with Korsakoff's syndrome. Heinemann stated that the clinical picture may be that of alcoholic intoxication. Morse expressed the belief that a psychic disturbance with stupor is often the outstanding feature. Elzholz stated that a confusional state is the usual type of mental disturbance.

It is usually rather difficult to establish clinically that a tumor of the brain is metastatic, for the symptoms referable to the cerebral lesion are often essentially the same as those presented by a primary tumor of the brain. Moreover, the primary lesion may be a silent one, or the cerebral symptoms may be so pronounced as to obscure the less obvious symptoms and signs referable to the primary tumor. At other times, especially if there is carcinomatous involvement of the meninges, the clinical picture mimics some inflammatory lesion or functional disturbance. At times, obtaining accurate data as to symptoms, signs, and laboratory studies essential in establishing a diagnosis, is precluded by marked physical and mental deterioration of the patient.

Careful general examination should be conducted in all cases in which there is a clinical picture of tumor of the brain. Any unusual clinical or laboratory observations should be investigated further. Thus at times, by the use of the bronchoscope, proctoscope or cystoscope, it is possible to demonstrate a malignant lesion outside of the central nervous system and thus probably to save the patient from an unnecessary and hopeless operation on the brain.

Roentgenograms of the head and thorax should be made as a routine in all cases in which tumor of the brain is suspected. There was pulmonary involvement, either of a primary or of a secondary nature, in 83 per cent of cases in this series in which necropsy was performed. Definite roentgenologic evidence of pulmonary disease was present in 51 per cent of these cases. However, in half of these cases the mistaken diagnosis of inflammatory lesion was made. Shelden has pointed out that, in searching for evidence of a primary malignant tumor outside of the central nervous system, such roentgenologic reports as healed tuberculous lesion, miliary tuberculosis, pleural adhesions, pleural effusions and pneumoconiosis should be received with suspicious reserve, and that reexamination should be made at frequent intervals to determine whether the signs are constant.

If possible, microscopic examination of tissue removed at operation in recent years should be made. Biopsy of enlarged lymph nodes, or of nodules in the skin, may disclose evidence of an extracerebral malignant tumor.

Tumor cells occasionally have been found in the spinal fluid, as in the cases of Schwarz and Bertels, Panton, Stadelmann and Meyer.

Frequently, the general appearance of the patient may furnish a clue to the diagnosis, especially if he is within the usual cancer age, if he has lost appreciable weight, or if he is at all anemic or cachectic. The usual history in a case of metastatic malignant tumor of the brain is one of precipitate onset and rapid progression of symptoms and signs, dissemination of objective signs due to multiplicity of lesions, and, from day to day, considerable fluctuation in intensity of symp-

toms and signs. This picture is frequently augmented by mental disturbance, especially of a confusional type.

Summary

The incidence of metastatic tumor of the brain is at least 5 per cent of all tumors of the brain observed at The Mayo Clinic.

There are focal (masses) and diffuse (encephalitic) lesions in the brain.

The primary malignant tumor was in the lung, breast or kidney in more than 50 per cent of the cases.

The primary lesion is frequently silent.

Metastatic tumors of the brain often present essentially the same syndrome as primary tumors of the brain.

All cases presenting clinical evidence of a tumor of the brain should be studied carefully for evidence of primary malignant tumor outside of the central nervous system.

In all cases in which there is clinical evidence of tumor of the brain roentgenograms of the thorax and skull, for evidence of metastasis, should be made as a routine.

Choked disks occurred in 40 per cent of the cases of metastatic tumor of the brain.

Multiplicity of lesions, and consequent dissemination of signs, may lead to the assumption that the cerebral manifestations are the result of inflammatory disease.

Mental symptoms, especially of a stuporous or confusional type, occurred in more than 50 per cent of the cases of metastatic malignant tumor of the brain seen at The Mayo Clinic.

The incidence and intensity of mental symptoms in this series of cases appeared to bear some relationship to the incidence of the encephalitic changes.

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Ephedrine in the Treatment of Narcolepsy*

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Cases of narcolepsy of various types have been described in the literature but no successful form of treatment had been recorded until Doyle's[12] recent report. In five cases of this disease the somnolent and cataleptic seizures were abolished within twenty-four hours by the use of ephedrine. In this paper I wish to present two other cases in which I have used this drug with the same success.

The first physician to write upon the subject of narcolepsy was Aretaeus who, in the first century, wrote two books upon "The Lethargics", Galen also referred to abnormal somnolence and lethargy in his writings. Dana[1] was able to find but fifty cases reported prior to 1878. Narcolepsy was first described by Westphal[2] in 1877, but was given its name by Gélineau[3] in 1880. However, Gélineau credits Caffe[4] with describing the first case in 1862. Fischer[5] reported one case in 1878.

Gélineau suggested the name of "narcolepsy" for "a rare neurosis characterized by an imperious sleep of sudden onset and short duration which recurred at more or less frequent intervals". At the present time when we speak of narcolepsy we recognize a distinction between those cases of prolonged somnolence which some of the earlier writers have reported and the true narcolepsy of today in which the diagnosis is based on two very important points, namely, that the conditions of narcolepsy and cataplexy must co-exist. Several German writers have recognized this distinction as did also Löwenfeld[6] in 1892, Camp[7] in 1907, Adie[8] in 1926, Kinnier Wilson[9] in 1928, Cave[10] in 1929, and Daniels[11] and Doyle [12] in 1930. In 1929, Cave of the Mayo Clinic presented narcolepsy as a definite clinical entity in his group of forty-two cases which was the largest single series reported up that time. He made the statement, "that narcolepsy is a rare condition is shown by the fact that these forty-two cases represent a total registration of 361,602 patients or one case of narcolepsy in every 8,610 patients".

Narcolepsy may be described as a clinical syndrome which consists first, of irresistible attacks of sleep which may occur at any time or in any place, and of variable duration lasting from a few seconds to several hours, and secondly, of cataplectic attacks which are characterized by a sudden transitory loss of muscular tonus which is usually precipitated by an emotional stimulus such as laughter, anger, excitement or exertion. During these cataplectic attacks the patient may lose complete power in the skeletal musculature and may fall to the ground in

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a perfectly helpless condition but in the majority of cases complete consciousness is maintained. These attacks are usually of short duration and following them the patient will be able to continue whatever he was doing before the attack. Occasionally he will merely experience the "shaky spell" without the precipitate fall and at other times only certain muscle groups will be affected rather than the entire muscular system. The narcoleptic and cataplectic attacks usually occur independently of each other. Frequently the patient will refer to the cataplectic symptoms as "shaky spells". He may complain of diplopia and dimness of vision as prodromal symptoms of the attack. Because laughing often precipitates an attack the German writers often refer to it as "lachschlag" or "laugh stroke". As Doyle has mentioned, perhaps it is the feeling of mirth rather than the laughter itself which precipitates the loss of muscular tonus. The disease is idiopathic but similar symptoms are not uncommonly associated with inflammatory or neoplastic diseases of the third ventricle.

Pathological changes which may occur in idiopathic narcolepsy have not yet been demonstrated. Somnolence has been noted for a long time as being associated with organic lesions at the base of the brain. As Cave has stated, the sleep of the narcoleptic patient is of a far different type than that of a patient with organic disease of the brain. Fulton and Baily[13] were of the opinion, after an extensive review of the subject, that sleep disturbance was the result of changes in the region of the gray matter near the Sylvian aqueduct. We may conclude from this and other data that narcolepsy is the result of a lesion in the region of the posterior portion of the third ventricle.

The etiological factors of narcolepsy are not known. It has been suggested that encephalitis, so common after the influenzal epidemic of 1918, might be a contributing factor. In Cave's series of cases, twenty-four out of the forty-two patients gave no history of encephalitis. Six of his cases were definitely post-encephalitic, and in twelve of them there was a history of influenza on an average of five years previous to the onset of the narcoleptic symptoms. It would seem, however, that narcolepsy has become much more common since the influenzal epidemic of 1918. Adie[24] was of the opinion that the family and personal history of the patient revealed no factors of etiological importance after reviewing fifty cases in 1930. Cave was of the same opinion. Camp, however, thought that it must be regarded as a mental defect. Gélineau speaks of it as a rare neurosis. Purves-Stewart,[14] Church and Peterson,[15] and others have been of the opinion that narcolepsy is hysterical in nature. I believe that narcolepsy cannot be explained on a functional or hysterical basis.

In Camp's series the sexes were equally affected and the age of onset was from ten to fifty-one years. In Cave's series thirty-four cases were in males and eight in females, a proportion of about four males to one female. The age of onset in males varied from nine to forty-six years. The duration of symptoms in males before examination by Cave varied from six months to twenty-one years. The age of onset in females varied from eight to thirty-seven years.

In 1907, Camp was of the opinion

that genuine cases of narcolepsy were not common in the literature. Adie, in 1926, stated that narcolepsy cannot be considered a rare disease. Cave's paper shows rather conclusively that it is a relatively rare condition when only one case is found in every 8,610 patients who were examined at the Mayo Clinic.

Cave's etiologic classification follows:

Idiopathic	23
After encephalitis	5
After infections other than encephalitis	3
Associated with hypothalamic syndrome	4
Associated with sleep attacks only	7
Total	42

Narcolepsy is essentially a chronic disease but the duration of the symptoms is unknown. Cave mentions four cases in which the patients had had attacks of sleep for fifteen, twenty and twenty-three years. Adie states that complete permanent recovery has not been observed.

Cases which often have been confused with true narcolepsy are those of hysteria, epilepsy, encephalitis, hypnosis, brain tumors, cerebral and arterial sclerosis, hypothalamic lesions, and the somnolent symptoms sometimes observed in obesity and in pregnant women.

The report on the two cases of narcolepsy examined and treated by me follows:

Case Reports

Case 1. A white male, single, 34 years of age, was examined on November 15, 1928. His family history was not significant. He had had the ordinary diseases of childhood. When I first saw the patient his presenting complaint was that of sleeping spells. He had been well in every way until 1918 when he was in the army and noticed that while drilling he would become very tired. As time went on he would fall over while drilling because of extreme weakness in his muscles. When he went in for mess at noon he would fall asleep and it was with the greatest difficulty that the sergeant could awaken him for afternoon duty. These sleeping spells increased in frequency and severity and his weak spells became more marked on exertion. He said that at times he would sink to the ground if he laughed or became excited. About two months after his trouble first started he was removed to a Government hospital where he was treated for a supposedly weak heart. At no time did he have any dyspnea or edema and he was not conscious of any heart trouble. As time progressed, he often fell asleep while eating, walking and driving a car. His general health remained very good. During the past few years this patient has carried on a gainful occupation as an insurance salesman but it has not been infrequently that he would fall asleep while talking to a client. He has had several automobile accidents lately as a result of falling asleep while driving and he said that it was not unusual for him to fall asleep while driving or walking home and to awaken when he was several blocks beyond his home. His sleeping spells will last for about half an hour and are usually preceded by a drooping of the eyelids and some dimness of vision. His narcoleptic sleep has been very deep and has been as common in the early part of the day as in the latter part. He has had very sordid and wild dreams shortly after going to sleep at night. He often thinks that snakes and mice are crawling about him and while asleep he will even pick mice from his body and insist that those near him take them from his hand. He resents being awakened from the dream state and at times has been somewhat pugnacious. He often dreams that the telephone is ringing and gets up to answer it. Since the onset of his trouble he has been unable to sit through a movie without sleeping during most of the performance and of late it has not been possible for him to drive a car at night.

The "shaky spells" as he calls them have continued to trouble him a great deal.

Laughter, excitement, anger or any emotional stimulus will bring on a shaky spell and if he is not able to grasp something he will sink to the ground. He has purposely avoided playing billiards because of these spells. The loss of muscular tonus or weakness is of very short duration in his case.

The patient's general physical examination was essentially negative except that he was slightly overweight and appeared to be somewhat dull. His eyelids drooped slightly. He answered questions with dispatch and there was no evidence of any neurotic tendency. He seemed to be ambitious and was very anxious to carry on his work. His blood pressure was systolic 140, diastolic 80, pulse 72, temperature 98.6°. The pupils were regular and reacted to light and accommodation. He has a small adenoma of the thyroid. His heart was normal in size, regular and the heart beats were of good volume. Examination of the lungs was negative. Abdominal and rectal examinations were of no importance. Neurological examination was negative. The fundus examination revealed nothing of significance and x-rays of the skull were normal. The urinalysis showed the specific gravity to be 1022, an acid reaction, no albumin, and no sugar, casts or blood. His blood count showed a hemoglobin of 80 per cent with a red cell count of 4,000,000 and a leucocyte count of 7,000. His metabolic rate was minus twenty on one occasion and minus eighteen on another. A Wassermann reaction was negative.

A diagnosis of idiopathic narcolepsy was made and the following treatment was instituted when the patient was first seen by me in 1928. He was given dessicated thyroid, grains 1 to 2, t.i.d; large amounts of coffee; and caffeine citrate, grains 1.5 to 2, t.i.d. He received absolutely no benefit from this treatment. Midway rest periods and sleep were tried and he would feel somewhat refreshed after these naps but for a short time only. As a matter of fact, the patient's symptoms have remained practically the same and his general health has not been impaired in any way since I first saw him in 1928.

In November, 1930, following the suggestion of J. B. Doyle of the Mayo Clinic, I started to use ephedrine for this disease entity. At the beginning of this treatment this patient's blood pressure, weight, blood count, urinalysis, fundus examination and neurological check-up were essentially the same as when I first examined him in 1928. His metabolic rate was minus seven which was somewhat higher than the previous tests.

This patient was given 0.375 grain (0.025 gm. of ephedrine on November tenth at five in the afternoon and 0.375 grain (0.025 gm.) at eight the following morning, at noon, and at four in the afternoon each day thereafter. Following his initial dose of the drug he drove his car for one hundred and fifty miles on a hunting trip against the wishes of some of his close friends who were afraid that he would fall asleep and swerve the car into the ditch. He stated that he did not have the slightest desire to sleep and was much more awake than anyone else in the party. He had not been able to drive a car at night for several years. He hunted all of the next day, walked a great deal, but had no sleepy or weak spells. He returned home on the following day and spent the morning working on his car, had his noonday lunch, read in the afternoon and attended a "movie" that night. He had no desire to sleep during the "movie".

This patient has continued to be symptom-free from both his narcoleptic and cataleptic spells. It is interesting to note that several days after he started the ephedrine he was required to drive to a nearby town about sixty miles distant. As he left the house he picked up a box which he supposed contained his medicine. When it was time for the noonday dose of ephedrine he opened the box and found that he had brought the wrong medicine along. He attempted to purchase some ephedrine but it could not be obtained. As a result he was forced to go without his medicine until he returned home that night. He got along fairly well in the early afternoon but stated that he had to pull off the road several times on the way home to sleep for ten or fifteen minutes. He has played billiards without any trouble and says that his night sleep has been much more restful and that he does not have horrible dreams as before.

I still have this patient under observation and it has been necessary to increase the

dosage of ephedrine from 0.375 gr. (0.025 gm.) three times a day to 0.75 gr. (0.05 gm.) three times a day in order to keep the patient symptom-free.

Case II. Is that of a boy, 13 years of age, who is perhaps overdeveloped mentally and physically for his age. He reported for examination on November 13, 1930, complaining of sleeping spells since the age of eleven years. These attacks were first noticed while he was riding in an automobile. As time progressed, he would fall asleep while in school or while eating. The spell would last for fifteen minutes to half an hour and he would be somewhat refreshed when he awakened. His night sleep was restless, he had sordid dreams and it was not unusual for him to get out of bed and walk about. His parents noticed that the weak spells in which he would fall to the ground were associated with laughter and exertion. After a few seconds or a minute he would be able to get up and would then be apparently normal. He tired easily and could not keep pace with other children of his own age in active play. He got along very well in school and was a leader in his class. His holidays were spent in sleeping for the most part and it was necessary for him to have an hour's sleep at noon each day in order to carry on his school work in the afternoon. It was not difficult to awaken him from his narcoleptic attacks.

The boy's family and personal history was negative. On general examination nothing significant was noted except that he was slightly obese and rather mature both mentally and physically. Basal metabolic reading was minus twenty when taken on two different occasions. His blood count and urinalysis were negative. His blood pressure was 100/80, pulse 72, temperature normal. Neurological examination was negative. The x-ray examination of his skull was negative.

I started treating this patient with ephedrine and he was given 0.375 grain (0.025 gm.) of the drug at 7:45 A. M. the same dosage at noon, and at 4 P. M. He was greatly relieved of his symptoms but continued to have occasional sleeping spells while riding in a car. He was able to enjoy a good joke and to play a game of football without having an attack of cataplexy. I increased the dosage of ephedrine to 0.75 grain (0.05 gm.) in the morning and at noon, and to .375 grain (0.025 gm.) at four in the afternoon. He felt even better under this increased dosage but had one or two attacks of narcolepsy while in his manual training class in school and also fell asleep for a very short interval while reading. The medication was then increased to 0.75 grains (0.05 gm.) three times daily. He now feels very well, is much more active, his night sleep is more restful, he is entirely free from the cataleptic attacks, and his parents say that they have noticed a remarkable change in the boy. He has had one or two short sleeping attacks.

The symptomatic treatment of narcolepsy has been without results untii Daniel's[11] and Doyle's[12] recent report in which they suggest the use of ephedrine. Camp[7] in 1907, Adie[8] in 1926, Brock[16] in 1928, Pearce[17] in 1928, Cave[10] in 1929, Common[18] in 1929, Levin[19] in 1929, Denyer[20] in 1930, and Ziegler[21] in 1930, all of whom have reported cases of narcolepsy, are agreed that the different forms of treatment which they have used have not been effective. These included dessicated thyroid, caffeine citrate, liquid strychnine, hormatone, pituitary gland, sedatives, deep roentgen-ray therapy, and regular intervals of rest in bed, the two latter measures having afforded slight relief.

To gain the best results in the treatment of narcolepsy, ephedrine should be given orally in doses ranging from 0.375 grain (0.025 gm.) to 0.75 grain (0.05 gm.), three times daily. The first dose is best given at eight o'clock in the morning, the second at noon, and the last at four in the afternoon. The last dosage is given early because Doyle has found that in some instances when the dosage has been given later in the day it has proved too stimulating

and the patient has complained of insomnia and restlessness. It has been my experience in the cases that I have treated that the night sleep has been much more restful since the patient has been taking ephedrine and that my patients have been practically free from the morbid dreams that are so frequently a part of the narcoleptic syndrome. I think that it is perhaps most advisable to start these patients on an initial dose of 0.375 grain (0.025 gm.) three times daily, and then to gradually increase to 0.75 grain (0.05 gm.) three times daily, if necessary. Doyle increased the dosage in one of his cases as high as 1.125 grain (0.73 gm.) three times daily, but the dose proved too stimulating for the patient. It appears to be very easy to establish the minimal dosage within a short period of time. There is the possibility that a slightly increased dosage of ephedrine may be required from time to time in these cases. So far as we know, there is no deleterious effect from the use of ephedrine in the amounts mentioned above.

Doyle says that "Chen and Schmidt,[22] and Johnston[23] commented on the occurrence of sleeplessness in certain persons following the use of ephedrine. More recently it has become common knowledge that ephedrine tends to abolish the narcotic effect of sodium iso-amylethyl barbiturate (sodium amytal) and that as an antidote to morphine it is more valuable than caffeine".

I feel that Doyle and Daniels deserve great credit for suggesting an apparently successful symptomatic treatment for the symptom complex known as narcolepsy for which, up to the present time, the medical profession has had nothing whatever to offer.

I believe that more time will be required to observe these patients who have been treated with ephedrine before final conclusions can be reached but so far the results in most instances have been remarkable.

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Typhus-Like (Spotted) Fever from Tick-Bite*

Rocky Mountain Spotted Fever Type; Identified with a Symbiont Proteus-like Septicemia

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CONSIDERING their world wide spread, and the toll of life they take annually, the typhus and typhus-like fevers are foremost among the grave fevers about which there is, at present, very little established concerning their microbic origin.[167] Consequently, specific therapy for these malignant fevers, so very urgently needed, has remained, and will perhaps continue to remain, contingent for its development upon discovery of more complete and exact facts concerning their microbic origin. Therefore, any data, even the least, should be made known in order that the typhus group of diseases may be placed on as complete and as scientific a foundation as the enteroidea group of fevers.

Although Rocky Mountain spotted fever has been demonstrated to be a different disease from typhus fever, it should be classed in the typhus group of fevers. According to observations by Spencer there is a febrile disease clinically indistinguishable from spotted fever of the Rocky Mountains but caused by a tick-borne virus that is not the virus of Rocky Mountain spotted fever.[196] Hence a sporadic case, although clinically indistinguishable from spotted fever of the Rocky Mountains, if originating remotely from an endemic area, and without obvious contact with ticks imported from an infected area, should be classed as a typhus-like fever from tick-bite of Rocky Mountain spotted fever *type* until such time as the virus causing the sporadic case can be positively identified to be that of spotted fever of the Rocky Mountains. This identification in our present knowledge can be made only from the patient's fresh blood (drawn during the fastigium of the disease), inoculated into guinea-pigs known to be susceptible to spotted fever, and into others known to be immune to spotted fever. As differential immunity tests have not been made with the virus of this case, the case will for the present be referred to as of Rocky Mountain spotted fever *type*, although clinically a typical case of that disease.

The purpose of this paper is to describe for the first time a case of Rocky Mountain spotted fever type originating in Missouri, midway between the original endemic area and the recently discovered eastern-southeastern states area;[217] secondly, to describe for the first time the clinical pathology of the

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spinal fluid in a spotted fever; and thirdly, to call attention for the first time to a virus pathogenic for man and maintained in nature probably as an antagonistic symbiont of a proteus-like microorganism.

A bacteriological and immunological study of this case has been prepared as a separate report.

Case Report

Unexpectedly, and under circumstances that made a complete bedside study out of the question, I was called upon to render medical care to a woman who was found, in time, to have a disease which I never would have supposed could come for observation within the locality in which I practice. Although the uncontrollable restrictions of time and the distant location of the patient's residence, made it impossible for me to do certain laboratory work, and to repeat some bedside examinations as often as I would like to have done, the clinical and bacteriological data obtained are of sufficient value to warrant publishing, especially in connection with the recent discovery of Rocky Mountain spotted fever in eastern and southeastern states, and the hitherto debatable observations concerning the nature of the virus causing spotted fever.[119 161 162]

The patient's demise, although certified as due to Rocky Mountain spotted fever, should not be interpreted in such absolute terms, as actually the patient had an advanced heart lesion (double mitral—nodal arrhythmia) and died a cardiac death; although in mentioning this fact it is not intended to minimize the severity of the infection, which was gravely prostrating from its onset, and hyperpyrexial after the third day. It has been said that no one over the age of fifty has been known to survive the malignantly virulent form of spotted fever to which this case has closest resemblance.[51]

Mrs. E. F., of Union Township, Marion County, Missouri, aet. 69 years, 3 mos., housewife; of naturally large and robust frame and musculature (known weight 166 lbs.), had resided on a farm practically all of her life and continuously so during the latter half. She bore three healthy children (no miscarriages) by first marriage. Her second marriage was subsequent to menopause, which was without event. Inured to heavy manual labor up to four or five years ago.

Previous Medical History. Four or five years ago she began to develop an arthritis deformans that involved chiefly the hands and knees with moderate severity and other joints to lesser degree. She had not considered herself habitually constipated prior to four years ago but following a hemorrhoidectomy a year and a half ago whatever degree of constipation there may have been became worse, necessitating the use of a saline cathartic every few days.

Cardiac insufficiency, first noticed about two and one-half years ago became worse and remained so following a "typhopneumonia" about eighteen months ago. "Pneumonia" (in late autumn—diagnosed by osteopath) lasted acutely for four or five weeks, and with convalescence for four months, was said to have been of severe degree, with considerable emaciation (this illness has a bearing on recently finding her serum to agglutinate *B. typhosus* in dilution of 1:80, partial in 1:160).

The patient had otherwise been well except for one attack of acute frontal and ethmoidal sinusitis about ten months ago. Since then she was semi-invalided due to cardiac condition and rheumatoid arthritis, but was nevertheless able to do most of her household and garden work the greater part of the time.

Present Illness. History of Tick-bite. During the morning of May 29th, 1931, patient walked near wooded hills to inspect some flooded fields in a creek-bottom. Late on the same day a "small, red, common woodtick" was discovered on her right foot, where it had engorged itself, about three centimeters proximal to the fourth metatarsal-phalangeal joint. The tick was removed and destroyed by a grand-daughter quite experienced in animal husbandry who later identified a live *Amblyomma sp.* as "being in all respects indistinguishable from the tick that was removed". Nothing was applied when the tick was removed, but mercurochrome, two per cent, was applied during

the evening of the day following as the site of the tick-bite was then itchy.

Incubation. Patient continued to feel well for seven and a half days, up to and including June 5, 1931, the afternoon of which day she made a trip to Palmyra, Mo., seven and a half miles distant, returning cheerful and without exceptional fatigue. Some vague malaise ("rheumatism getting worse") was perhaps noticed before retiring on June 5, although she slept the forepart of the night, but only brokenly and with restlessness during the latter part, which for her was quite unusual.

Onset. The following morning, June 6, Mrs. F. arose at 5:30 A. M. with a dull frontal headache, a pain in the left side of neck, and discomfort through her right hypochondriac region. She milked several cows but as malaise became rapidly worse and a sense of muscular weakness developed, with pronounced dull (deep drawing and boring) pains in extremities, particularly in biceps brachii, flexors of hands, hamstrings and crural muscles, she kept in bed from 6:30 to 8:30 A. M. but again got up and tried to do her housework. About 10:00 A. M. she took to bed with sudden profound chilliness (the day being warm). Chilliness was constant, exceedingly pronounced and was felt about equally over entire body, with absence of 'creepy feelings'. She probably did not have a true rigor but "no amount of bed-clothes and hot water bottles could get her warm". Chilliness continued unabated for four hours and then passed away slowly between 2:00 P. M. and 4:00 P. M. About 5:30 P. M. and again at 6:30 P. M. she vomited (a unique experience for her) and continued to feel nauseated for two hours thereafter. About 7:00 P. M. she had what was thought by relatives to be 'a heart attack' and I was sent for about 7:30 P. M.

Invasion (end of first day). I first saw patient at 8:30 P. M. at which time she answered questions readily, pertinently, coherently, and without retardation. Her temperature was then 102.4° F., pulse 112, respirations 22. Chief complaints were prostration (two days duration), pain in flexor muscles and vaguely in right diaphragmatic region. Slight cough (quite unusual to her) had developed during the latter part of the day but there was no pain in chest or on deep inspiration, nor sense of thoracic constriction.

Initial Physical Examination. Eyes, ears, nose and throat were negative; she was edentulous and without struma. Chest was negative; abdomen was not distended nor tender to palpation. No cutaneous lesions except scabbed over tick-bite (to which no significance was attached). Cutaneous tache was without urticarial element but blanching with peripheral erythematization was exceedingly pronounced. Mobility of neck and reflexes were normal. Blood pressure: systolic 155 (all beats at 150); diastolic, 108. Hemoglobin, 80 per cent. Heart murmurs were faint and inconclusive but were suggestive of double mitral lesion. Some nodal arrhythmia was present. Heart was transversely enlarged from 4 cm. left of left nipple line to 5 cm. to right of right sternal margin. Patient was slightly obese; tissue turgor was satisfactory.

Initial Impression and Therapy. Temperature was tentatively ascribed to nasal sinusitis and subacute cholecystitis or enteritis following constipation and a dietary indiscretion, although a beginning pneumonia was considered possible (due partly to it then being said, somewhat erroneously, that she had had a 'typho-pneumonia' at the same time a year previously). Saline catharsis (effectual at 10:00 P. M.) and a hypnotic (sodium amytal, grains three, every four hours, if necessary) were prescribed, and tincture of digitalis (LaRoche) was commenced in dosage of 24 drops regularly every four hours.

Patient slept for one hour after first dose of sodium amytal but not after second dose, four hours later.

Second Day, June 7th. During early morning, restlessness, fever (to 103° F.) and muscular pains having increased, I was called on by her son, and sent by him, sodium salicylate in raspberry elixir, grains twelve, every four hours, with instructions to take patient's temperature every three hours. Temperature continued absolutely constant at 103.2° F. during the second day without improvement in subjective symptoms. Patient coughed occasionally without difficulty, a little thin, clear mucus being

brought up. She cared for no nourishment but took orangeade and lemonade during afternoon without emesis. She slept not at all that night despite sodium amytal grains three every three hours.

Third Day, June 8th. Early in the morning I was called to the farm immediately following a sudden change for the worse observed about 6:30 A. M., or about 48 hours after onset of the disease. I found patient stuporous although arousable, but unable to articulate answers to questions which she seemed to understand, and wished to answer to priest and myself. On command she could not protrude her tongue. At that time temperature was 103.6° F.; pulse 98, respirations 24. Leucocyte count was 11,000. Fluids, no longer taken through glass tube, had to be fed to her with a spoon, but were swallowed with some slight difficulty.

Description of Skin Lesion. At that time, 7:30 A. M., patient was observed to have over her lower limbs, flanks, and forearms (including wrists and backs of hands) a rash of medium profuseness, stated by relatives to have been first observed by them about 5:30 A. M., which would have placed its appearance about 48 hours after onset of the disease. When first observed by me on lower limbs and forearms there was over abdomen, chest and back an evanescent marmoraceousness which before long gave place to pinhead sized macules of dull ham (tawney) color that in a few minutes increased in size and remained permanently. After an hour or so the lesions became progressively more cyanotic or mulberry colored as they increased in size.

Skin lesions were mostly discreet oval or ovoid, split pea to lentil sized, compressible (to fawn color through diascope) and non-indurated macules, for most part being not raised or only slightly raised above skin level. The macules, irregularly distributed and very slightly morbilliform, had their long axes paralleling the cleavage lines of the skin. The color became a dull mulberry red at times but usually was more cyanotic (violaceous) and never was as intense and as red as in meningococcus meningitis. For brief periods the rash lightened to a faint cyanotic hue but never disappeared entirely.

The rash spread upward over abdomen, chest and back during the course of the morning and new lesions appeared on the extremities but the neck and face were at all times spared except for a dusky blush over forehead. The face was then a little puffed and had a lemon tinge over malar eminences but no icterus was visible in the conjunctivae.

The conjunctivae were then very pronouncedly injected, and remained so throughout the third day, but lachrymation was not present. Photophobia pretty certainly was present but on account of the woman's stupor it was not an outstanding symptom. The tongue was moist, a trifle swollen and lightly covered with a white coat down the center. The pharynx was spottily injected and the patient continued to cough at intervals of a half hour or so, but no macular lesions were observed on the palate or buccal surfaces.

As patient had not voided for over twelve hours, and apparently could not do so she was catheterized every twelve hours, 800 c.c. being drawn off the first time, but the subsequent amounts diminishing by about one hundred c.c. each time. The results of urine analysis and other laboratory work will be described following history.

Although patient was always a trifle cyanotic, her chest continued without evidence of pleurisy or pulmonary consolidation, which with the low white count, stupor and spotted eruption, made me wish to exclude cerebro-spinal meningitis, despite the then well marked clinical picture of typhus fever.

The temperature curve, which from the first had continuously risen without a remission of more than 0.2° F. to a plateau of 103.6° during first half of third day, rose to 104° (axillary) during the afternoon (104.2° in early evening) of the third day, despite more or less constant cool sponging of upper two-thirds of body. Temperature (taken since morning by axilla) was charted at hourly intervals and showed a drop of 102° at 11 P. M. towards close of third day, but during night rose to 104° at 5 A. M.

Medication during the third day consisted of tincture of digitalis, increased to drops thirty-two every four hours, and as a detergent for mouth, upper intestinal and urinary tracts, about twenty grains of sodium sali-

cylate in ten ounces of water given in teaspoonful drenches at five to ten minute intervals, patient then being no longer able to swallow without difficulty.

When seen by me at 10 P. M. towards the end of the third day of disease, pulse was slower (84) and stronger; respirations 22, regular, of good excursion and without difficulty but with faintly audible inspiratory and expiratory wheeze. The patient was still coughing occasionally, but less frequently; chest negative for areas of consolidation (including posterior bases). Temperature 103.6° dropped to 102.2° an hour later, as mentioned above.

A daughter residing at a remote distance, who arrived at 7:00 P. M. was unquestionably recognized by patient who could not, however, be aroused from stupor easily, nor kept aroused for more than fifteen seconds at a time. Occasionally the patient tried to give expression to some discomfort in lower extremities but was unable to make coherent sounds or gestures, or to turn herself in bed. A coughing spell caused patient to void a little urine, expel flatus and soil herself with a small amount of semi-solid feces (having previously done so about two hours before). Abdomen was neither scaphoid nor distended, flatus having been passed during coughing spells. Spleen was palpable, firm but not hard, and extended four fingers breadth below costal angle.

Sodium amytal (about grains five floated on water) was later reported to have quieted patient a little during the third night.

Fourth Day, June 9th, patient had a 'sinking spell' in early morning and I was summoned to house. At 8 A. M. temperature was 103.4° (axillary), pulse 82, respirations 22. Pulse was weak but regular. Oxygen with oxygen-carbon dioxid rebreathing revived heart action. Injection of conjunctivae was noticed to have passed away almost completely. Stupor was deeper, patient being not fully arousable, but no evidence of delirium. Flexion of neck restricted but not rigid; patient habitually rolled head to left side. She moved arms with apparent vague purposefulness but ineffectually. Cried out faintly as though in pain when moved, catheterized, and given bed care.

The pulse having been revived, the morning was devoted to lumbar puncture, bedside laboratory work, and practically continuous cool sponging, the digitalis being continued.

Telegraphic request for Rocky Mountain spotted fever vaccine was made to the Secretary of the Montana State Board of Health but Dr. W. F. Coggswell promptly telegraphed back that vaccine was not used therapeutically.

During the fourth day the skin became cool and clammy and the tissue turgor very much reduced. Cough abated and swallowing became almost impossible.

Later Aspects of the Rash. The rash during the fourth day became somewhat confluent in a few places on the back, buttocks, and lower lateral aspects of thorax, abdomen and hips, but nowhere did the blotches exceed an area of one by two centimeters. Interstitial (purpuric) hemorrhage to a grossly noticeable degree was observable in not over ten lesions, chiefly on the distal portions of the flexor surfaces of the extremities. Neither confluence nor purpura were, on the whole, striking characteristics of the rash.

A few new lesions may have appeared during the fourth day but if they did so they did not attract notice.

Not all of the lesions increased in size during the fourth day but after twenty-four to thirty-six hours from the appearance of the rash there was a larger proportion of lenticular and large lenticular lesions than during the day before, the spots being more distinctly visible at a distance, and permanently a more livid blue. Towards the latter part of the fourth day most of the macules were slightly sunk below the general level of the skin, and most of them (except in dependent portions) towards the end of the day took on an ashen blue, 'washed out' appearance.

When patient was seen by me at 10:00 P. M. the pulse was found to be 136 and thready, the temperature having fallen to 102.6°. The patient was breathing without much difficulty, rate 24, but tracheal rattle was present. Venipuncture was attempted but only 16 c.c. of blood was obtained due to collapsed condition of veins. During the

night the pulse became imperceptible and patient expired at 7:20 A. M. on the morning of the fifth day, or about ninety-six hours after onset of definite symptoms of malaise, or about one hundred and eight hours from first prodromata.

The temperature readings (axillary) of the last twenty-four hours were as follows: June 9, 6:00 A. M., 103.4°; 6:35 A. M., 103°; 10:00 A. M., 103°; 11:30 A. M., 103.6°; 2:35 P. M., 103°; 3:30 P. M., 104.4°; 5:10 P. M., 105°; 5:40 P. M., 104.4°; 6:25 P.M., 104.2°; 7:00 P.M., 103.8°; 8:10 P. M., 104°; 9:00 P. M., 103.8°; 10:00 P. M., 102.6°; 11:00 P. M., 102.8°; midnight, 102.8°; June 10, 1:30 A. M., 103°; 2:15 A. M., 103°; 3:00 A. M., 103.4°; 4:00 A. M., 104°; 5:00 A. M., 104.8°; 6:00 A. M., 104.8°; 7:00 A. M., 103.6°; exitus at 7:20 A. M.

Laboratory Examinations

Blood. White cell counts: at 12 hrs. after onset, 11,000; at 48 hours, 11,200; at 72 hours, 7,300. *White cell morphology* (72 hours). Cells took Wright's stain well, cytoplasm staining somewhat more intensely bluish than normal. Numerous polymorphs were quite large due to increased cytoplasm, and were somewhat ameboid in outline, but no polymorph or large mononuclear was found to have cell inclusions except rarely a few polar staining bacilli of Proteus type as described more fully in accompanying section on bacteriology. Although frequently it seemed as though the bacilli were in the leucocytes, in the majority of instances they were lying on the outside of the leucocytes.

Differential counts:	Baso.	Eos.	Jung.	Stabs.	Segments	Lymph.	L. Mono. Trans.
at 48 hrs. after onset	0	0	3%	7%	61%	20%	9%
at 76 hrs. after onset	0	0	5%	8%	56%	20%	11%

Red cell counts: at 7th hour: 4,100,000. Color index 1. *Hemoglobin*: 80 per cent (Talquist). *Clotting time*: (needle drag method) at 48th hour, 2.75 min.; at 76th hour, 4.5 min.; at 88th hour, 8.25 min., with serum deeply tinged with hemoglobin.

Agglutination tests: (National Institute of Health—letter of June 15, 1931 by R. E. Dyer) Agglutination of *B. proteus* X_{19} positive in dilution of 1:20, partial in 1:40. Agglutination of *B. typhosus* positive in dilution of 1:80, partial in 1:160. (See history in regard to typhoid fever 18 months previously). A typhoid agglutination made from partially dried, diluted serum drawn about the same time as that submitted to the National Institute of Health was reported negative by St. Elizabeth's Hospital, Hannibal. Agglutination tests were made on blood drawn at the 88th hour of the disease.

Organisms: Proteus-like organisms were first observed in the blood 48 hours after onset but no significance was attached to them as they were considered contaminations from the finger although the latter had been well washed with alcohol. Minute diplobacillary (and diplococcoid) organisms were observed in fresh and stained specimens of blood drawn 76 hours after onset, and a few proteus-like organisms were also observed as on the preceeding day. Similar organisms having been found at the same time in the spinal fluid (microscopically free from more than a very occasional, isolated red blood cell) some attention was paid to looking for granules and motile organisms but none were accepted as being motile (Brownian movement being taken into consideration) during the few minutes then at my disposal for such examination. Subsequent experience has convinced me, however, that there were minute motile (bacillary and diplobacillary) organisms then present. More numerous diplococci were found then than on the previous occasion.

Blood drawn under the most rigid aseptic precautions at the 88th hour of disease (10 hours before death) was sealed in sterile tubes (kept at room temperature, about 62° F.) and examined fourteen hours later, at which time the blood was found to harbor mature motile, proteus-like organisms, also numerous minute diplobacilli (rickettsia-like) organisms as well as diplococci and refractile granules. The latter were found adhering chiefly to the diplococci and diplobacilli although some granular structures were observed adhering to the erythrocytes but as they here appeared dark instead of

refractile it was not clear whether they were monococcic forms of the diplococci or the granules associated with the latter. The mature proteus-like organisms were too motile to determine whether any granules were adherent to them, but a close study of stained blood smears indicated that these granular bodies must unquestionably have been within their surface tension area when they were motile. At that time I was not familiar with the work of Ricketts, Wolbach, Cowdry, Nagayo and others, and was disposed to regard the granules as "blood dust" and the proteus-like organisms as a terminal invader. However, subsequent studies, forming the basis of a bacteriological report to be made shortly, have convinced me that the "granules" in all probability constitute the virus of Rocky Mountain spotted fever.

Erythrocyte Morphology. Unstained thick whole, thin whole, dry films, and unstained moist chamber films were examined as well as dried films stained with Giemsa's stain and with Wright's stain, Gram's stain, polychrome methylene blue, etc. Several hours search under the oil immersion (x1100) permitted drawing the conclusion that no organism could be found within the erythrocytes. The same basal (chromatin) staining, ultramicroscopic granules (monococci ?) could be found in relation to the periphery of the red blood cells as mentioned above for the proteus-like organisms. In most instances the granules, which were a little angular in outline (wedge-shaped) appeared to be in contact with the surface of the erythrocytes; they were mostly nonmotile, but once a granule was seen to have a changing relation with respect to the erythrocyte; whether this was due to movement of a current in the moist chamber, or to motility originating in the granule, it was impossible to tell.

Stipple-celled degeneration, anisocytosis, poikilocytosis, fragmentation. etc., were not observed up to the 88th hour. The sedimentation time was not observed.

Cerebrospinal Fluid. Lumbar puncture (at 76th hour of disease). Small amount (6 c.c.) of fluid was obtained unmixed with the least macroscopic trace of blood. Spinal fluid was under no increased pressure and came away only by drops at three or four second intervals. Crystal clear as drawn into sterile bottle and sealed.

Cell count, on blood counting chamber: numerous fields were examined and averaged at 5.3 cells per c. mm.

Reducing substance absent (0.5 c.c. used); boiled in three times the amount of Benedict's qualitative test solution. *Albumin* increased. Amount roughly estimated to be three of four times normal. *Globulin,* Pandy's test, not increased.

Red blood cells very occasional (under one to a field). Hemorrhagic encephalitis definitely excluded.

Organisms. In fresh spinal fluid used for making the cell count a few proteus-like and di-coccoid organisms were observed under high power objective, but no diplobacilli. However, what attracted my attention were groups of exceedingly minute, barely visible, refractile granules too dispersed to constitute even a pseudo-morula, yet suggesting a community. The granules were not entirely scattered at random but all granules could not be associated with groups. When fresh cerebrospinal fluid was examined under the oil immersion (x 1100) these granules were found to vary in size by about 100 per cent in diameter from smallest to largest, the largest being less than half the diameter of the di-coccoid (or diplococcoid) phase of the proteus-like organism. The granules were not mobile nor was there noticeable movement of or within the colony, which resembled the appearance of a constellation of stars on a bright night.

Fresh cerebrospinal fluid concentrated somewhat by low heat on a bacteriologically clean slide and stained by Wright's and by Giemsa's stain showed numerous mature proteus-like organisms, with polar staining well marked, rickettsia forms in chains of twos and threes, and what appeared to be masses of granular detritus around them. As the latter took the chromatin (polar) staining as well as the polar and band-like masses in the mature proteus-like organisms, the granules were presumed to be bacterial extrusions or nuclear fractions of disintegrated proteus-like organisms. The granules were not pin-point round but had a variable three-cornered rounded angularness or wedge

shape. No micrometer measurements could be made at the time, but the largest granules were estimated not to exceed 0.12 micron in largest diameter.

Urine. Catheterized specimen at 48 hours after onset (12 hr. A. M. specimen). Amount, 800 c.c. Color, deep amber; colloidal cloudiness becoming flocculent. No bacterial haze; no bile. Sp. gr., 1.022. Reaction acid to litmus. Albumin, large trace. Sugar absent. Microscopically free from pus cells and crystals. Some epithelial cells from bladder.

Catheterized specimen at 72 hours after onset (12 hr. A. M. specimen). Amount, 600 c.c. Color, dark amber; colloidal cloudiness becoming flocculent. Suggestion of bacterial haze. No bile. Sp. gr. 1.030. Reaction, markedly acid to litmus. Albumin, very small amount. Sugar absent. Microscopically free from pus cells and crystals; epithelial cells from bladder more numerous than on preceding examination. Occasional red blood cells. Numerous motile bacilli now seen for first time, type not identified.

Animal Inoculation

Blood drawn at the 88th hour of the disease and kept sealed in a sterile container at room temperature (62° F.) was injected 22 hrs. later into a female guinea-pig. The injection was made at St. Elizabeth's Hospital, Hannibal, Mo., at 8:30 P. M. on June 10, 1931. With sterile syringe 1 c.c. of patient's (imperfectly clotted) blood was drawn into 2 c.c. of sterile water and mixed in the syringe and then injected intraperitoneally into a guinea-pig weighing about 220 gms. Only 2.4 c.c. (0.66 c.c. of blood) was injected due to plugging of needle. The guinea-pig was found dead about eleven hours later.

When necropsied twelve hours later the guinea-pig was found to have a markedly swollen, erythematous vulva and hemorrhagic foci in all foot-pads of three feet, but no cutaneous lesions. The puncture had done no injury to the intestines or to a large blood vessel, and there was no evidence of peritonitis. Several areas of thickly studded "pin-point granulations" on the parietal and visceral peritoneum were noticed but not at that time realized to be a manifestation of fatal spotted fever in the guinea-pig.

From the small amount of thin, sanguinous fluid in the peritoneal cavity, smears were made and stained with Wright's stain. The smears showed only very occasional proteus-like organisms that took the stain very poorly. It seemed, therefore, likely that these organisms did not proliferate in the guinea-pig, and were not the cause of death.

Diagnosis

Apart from virus studies of this case, preliminarily reported above, the differential clinical study should take into account typhus fever, meningococcus meningitis, typhoid and the paratyphoid fevers, a streptococcus septicemia and spotted fever of the Rocky Mountains. If the fever had been contracted in certain other localities it would be necessary to consider the septicemic type of plague, to say nothing of certain Asiatic and tropical fevers.

The meningococcic and pneumococcic meningitides can be unequivocally excluded by the clear spinal fluid, not under pressure, and the absence of the characteristic and easily recognizable organisms of those diseases.

Typhus fever can not be excluded on clinical evidence alone. Indeed typhus was given serious consideration about the forty-eighth hour after onset, and it was only the history of tick-bite, the more abrupt and quicker, more malignant clinical course, and profuse lenticular macules (larger and more cyanotic than usually occur in typhus) that decided in favor of Rocky Mountain spotted fever. In this connection is to be noted that *Proteus* X_{19} was agglutinated in dilutions of 1:20 and partially in 1:40, but this, the Weil-Felix reaction, is known to occur in Rocky Mountain spotted fever[128,217].

Streptococcic septicemias of malignant character have occurred in my practice and have, of course, been noted to cause petechial eruptions, but the febrile course has always been very irregularly remittent (septic type) and the peliosis has been hemorrhagic (purpuric) from the instant of first appearance, especially never fading under the diascope. Besides, the petechiae come out only in small numbers at a time, at random, the face and neck not being spared and the spread of the eruption is not rapid and orderly like an exanthem, as in spotted fever.

Typhoid fever with typhus-like course occurs occasionally and a case of such sort could not be unequivocally excluded by clinical appearance alone. Also is to be noted that the patient's serum was reported to have agglutinated *B. typhosus* in dilution of 1:80 (partial in 1:160) although by one observer it was reported negative in blood drawn at same time as that from which the quasipositive report was obtained. In this connection is to be observed that the patient probably had a case of typhoid fever about eighteen months previously. The rapid pulse, moist anemic, swollen tongue, firm spleen, absence of abdominal distention and urine without a well marked bacterial haze were not conformable to typhoid fever in even an early phase.

Over and above the history of tick-bite, and the virus (with a rickettsia-like phase) obtained from the blood and spinal fluid, the character of onset, steadily rising unremitting fever, very pronounced injection of the conjunctivae without lacrimation, and the typical muscle pains associated with the type of eruption would be sufficient to establish a clinical diagnosis of Rocky Mountain spotted fever.

For the history, symptomatology and clinical types of Rocky Mountain spotted fever see the author's paper "Mountain Fever and Spotted Fever of the Rocky Mountains—Clinical Studies".

Brief Correlation with Previous Investigations

Spotted fever of the Rocky Mountains was first described clinically in 1896.[1] Clinical differences between the virulent form in the Bitter Root Valley and the more benign form in Idaho were described between 1898 and 1902.[2,3,9,14] An intermittent form, very probably however a separate disease, was described by Kieffer in 1907.[35]

Wilson and Chowning focussed attention on the transmission by a tick,[5] but mistook artifacts for piroplasms.[27] Anderson supported the tick theory and found in the blood, during the disease, diplococcoid organisms that resembled forms encountered by me.[11] Stiles, who had attacked the tick theory in 1905,[22] described the common vector, *Dermacentor andersoni*, in 1908.[42] McCalla and Brereton in 1905 transmitted the disease by tick-bite to man,[37] and in 1906 King[24] and Ricketts[29] transmitted the disease by tick-bite to guinea-pigs.

Chowning in 1908[34] described, as the cause of the disease, but on inconclusive evidence, a proteus-like organism similar to the one recovered by me and shown by me to be non-pathogenic.

Ricketts succeeded in maintaining the virus in the guinea-pig[25] and showed that it was non-filterable,[26] later confirmed by Spencer and

Parker.[145] Ricketts incriminated minute, uncultivatable diplobacilli (rickettsiae) which he found were transmitted from one tick generation to the next through the eggs.[55] Moore in 1911 showed that the tick did not infect at once but required 1.75 hours to infect a guinea-pig and that it required about ten hours of feeding for a tick to acquire infectiousness from a guinea-pig.[71] Maver showed that ticks other than *D. andersoni* could transmit the disease.[73]

In 1907 wild rodents, which had been suspected as being the natural reservoir of the disease were found to be susceptible to it.[33] Studies by McClintic, who lost his life in investigation of this disease, had to do chiefly with the disease in nature and the institution of control measures by clearing underbrush, destroying small wild life, etc.[79]

Bacteriological work done by Mitchie and Parsons in 1916 showed that the virus could not be recovered by the cultural means then available.[96]

On presumptive but very equivocal evidence, Wolbach in 1918 described Rickett's diplobaccilli as the virus[102] and obtained some growth of these rickettsiae in tissue cultures.[127] Noguchi later failed to isolate a virulent rickettsia from known infected ticks but did show that three strains of rickettsiae from such ticks were not pathogenic,[161] whereas a filter-passing virus could be obtained from *D. andersoni*.[162]

The most significant recent developments have been the demonstration of the spread of the disease in the Rocky Mountain and adjacent states,[136,203] the development by Spencer and Parker of a practical vaccine from ground-up infected ticks[153,199] and their studies of the virus.[145,197] Spencer and Parker showed that the virus has a latent, immunity producing phase and that to acquire virulence it requires reactivation, which occurs during the process of engorgement of the tick.[139] They also showed that the virus was not thrown down by high speed (8800 R.P.M.) centrifugalization, and that it could not be separated from the red corpuscles and white blood cells by repeated washings.[158]

The most important recent developments have been the discovery of transmission in nature by means of the rabbit-tick,[131] the introduction of tick parasites,[183] the further demonstration of the utility of the Spencer-Parker vaccine,[209] and the demonstration of the disease in an eastern and southeastern states endemic area by L. F. Badger, R. E. Dyer and A. Rumreich.[216,217]

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Post-Pneumonic Lung Abscess Resembling Lung Tumor*

With Case Report

By George F. Cooper, M.D., Lieutenant, Medical Corps, United States Navy, *Canacao, P. I.*

IT IS difficult to differentiate an unresolved pneumonia from an encapsulated empyema in which the retained fluid is under pressure. It is also difficult, at times, to differentiate either of the two conditions mentioned above from a lung tumor. It is usually necessary to take into consideration not only the physical findings and x-ray examination, but the history of onset before an absolute diagnosis can be made.

Middle lobe pneumonia, without involvement of the remainder of the lung, is a rare condition,[1] and may terminate in various ways. It may resolve and clear up in a very short time, or it may go on to suppuration and gangrene. The condition may also break down into abscess formation and this collection of pus be later evacuated into a bronchus and drained. The case reported is believed to be one of the latter type.

It is an unusual case and was variously diagnosed as malignancy, encapsulated empyema, lung abscess, and finally a resolving pneumonia.

Figure 1 shows the first x-ray taken before the pus was evacuated. The density of the shadow very closely resembles that of a lung tumor. At that time percussion over the area gave a total dullness. Breath signs were entirely absent. During the night the patient had a series of severe coughing spells and began to expectorate large quantities of a purulent greenish pus, which was without the odor usually associated with lung abscess.

The next morning the area was aspirated and nothing could be withdrawn. Another x-ray was taken (figure 2), and it was found that the area in the right lung had changed slightly in density and outline. The top border appeared flattened rather than dome-shape. The patient was then allowed to rest for a few days.

At this time breath sounds were beginning to reappear over the mass, and a third x-ray (figure 3), was made. This latter suggested a resolving pneumonia, with a suggestive area in the center of the mass which resembled cavity formation.

The patient continued to cough up quantities of purulent material for several days, but this gradually decreased in amount and finally disappeared.

During the night in which he first

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began to expectorate pus from the lung, his temperature was 103.8° F., but this dropped to 97.6° F., by morning and has been normal since. His leukocytes at that time were 14,600 with 64 per cent polymorphonuclears. Pulse at no time had gone over 100 since day of admission to hospital and respirations had been normal at all times.

Since this patient gave a history of illness with pain in left chest for three months, it is believed that he had a pneumonia at one time which left a collection of pus either in the middle lobe of the right lung, or an encapsulated empyema between the upper and middle lobes.

While the x-ray in figure 1 resembled a pneumonia, the pulse, respiration and leukocyte count were all against such a diagnosis. The mass was sharply outlined and the dulness on percussion such that a diagnosis of malignant tumor seemed justified. The patient's general condition was not good, and he gave a history of having lost considerable weight over a period of three months.

His most constant symptom during that three months was pain. This was

FIG. 1. First x-ray taken on January 20, 1931.

FIG. 2. X-ray taken on January 27, 1931, showing slight decrease in density and size of area.

so severe that he walked in a bent over position. He had no difficult in breathing and stated that he noted no fever at any time. He was not coughing at time of onset and had no coughs or colds previously.

Sputum examinations have been consistently negative for acid fast bacilli, the only abnormal finding being many pus cells and two organisms in abundance, one of which resembled *B. influenzae*, and the other a short chain streptococcus. Pneumococci were noted once.

Immediately after expectoration from the lung began to increase, the pain in his chest became less, the patient felt better, began to gain in weight, and in a few days was symptom-free. The illustrations are from x-rays taken at different intervals as mentioned and show his condition at the different stages of his illness. The case history and laboratory findings are given in detail below. Chart 1 shows the temperature, pulse, and respiration with the drop in temperature during the night of the twenty-third when the abscess began to evacuate.

FIG. 3. X-ray taken on February 6th, 1931, showing considerable decrease in size and density of area in lung, with a suggestion of cavity formation.

CASE REPORT

January 19, 1931. P.A.B., a white male, age 33, well developed and fairly well nourished, admitted to medical ward complaining of severe pain in right side of chest, which he states has been present for three months.

Past History. This is the third attack of the same condition in the past three months. Has had a continuous temperature with night sweats and coughing in the early morning. Contracted syphilis in 1926, but has had adequate treatment.

Family History. Father dead at 62, heart disease. Mother dead, cause unknown. Two brothers and one sister living and well. No history of cancer, insanity, or tuberculosis in the family.

Physical Examination. Eyes, ears, nose and throat negative. Heart negative. Lungs: Coarse râles over areas of both lungs, and areas in right lung suggestive of small cavity formation. Patient is suffering from considerable pain in his chest at present, especially when he coughs. There is an area of dulness over the entire middle lobe, right lung. Examination otherwise negative.

X-ray of chest, shows a mass which occupies practically one-half of the right lung (figure 1). While this patient has had syphilis, it is not believed that the condition in his lung is a luetic infection. Kahn test is negative and has been for the past year.

Laboratory Data. Leukocyte count: 11,300.; neutrophiles, 64%. Red blood count, 3,900,000. Hemoglobin, 70%. Urinalysis negative. Kahn test negative. Sputum negative for acid fast bacilli on several occasions, but shows a few gram-positive diplococci, many short chain streptococci, and an abundance of small bacilli, morphologically resembling *B. influenzae.*

January 22, 1931. Leukocytes 14,600. Polymorphonuclears, 66%.

January 24, 1931. Patient had a severe coughing spell last night and began to expectorate copious amounts of purulent sputum. Temperature dropped during the night. Taken to surgical ward and lung aspirated, but no free pus obtained, probably on account of drainage during the night.

January 25, 1931. Temperature has remained down and patient feels much better. Pain is less. Coughs considerable but it is a productive cough. His condition appears to be either a walled-off abscess occupying the entire middle lobe of the right lung, or a malignancy. The x-ray shadow under the fluoroscope is almost as dense as the heart shadow.

January 25, 1931. X-ray of this date shows a suggestion of lessened density in the mass with a change in the outline at the top border. The lower border is ragged and appears to be attached to the diaphragm which is higher than normal on that side. Of course, the right side of the diaphragm is normally higher than the left, but this appears to be even more so, and under the

FIG. 4. X-ray of chest made February 14, 1931, showing almost complete resolution.

fluoroscope, to move with the mass in the lung.

Stereoscopic plates show the condition to be very close to the chest wall anteriorly, and close to the surface of the lung.

January 26, 1931. Temperature 98.8° F. Has slight pain. Cough is still productive of much purulent sputum. The sputum has no odor as would be expected from a lung abscess. Patient has no history of coughs, colds, or other illness prior to the onset of the present condition, the first symptom of which was pain in the chest, three months ago.

January 27, 1931. Examination this date shows a lessened density of the area involved with increased breath sounds. Mass does not seem so sharply outlined on percussion. X-ray taken in standing position at 36 inch distance shows a decreased density of the area with a beginning resolution in the center, which seems to be clearing up. Top border has changed in appearance. Instead of a convex border it is now concave. Total area is noticeably decreased in size. Patient continues to expectorate considerable purulent material. Lung at this stage suggests a resolving pneumonia. The part of the lung involved corresponds almost exactly with the outline of the middle lobe, right lung.

January 31, 1931. X-ray of chest shows decrease in density and size of area in right lung, with adhesions downward and towards the hilum.

Further questioning of patient as to onset of illness reveals the following information:

"At time of onset his bones ached and he

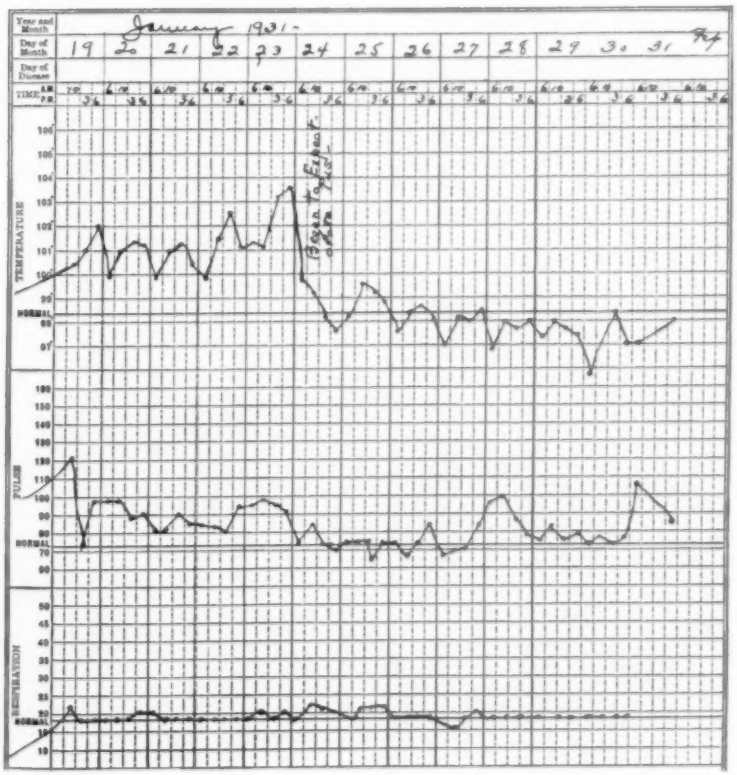

CHART 1. Temperature, pulse, and respiration graphs. Note sharp fall in temperature with evacuation of pus by expectoration.

felt very weak. His chief complaint was pain even on pressure outside the ribs of his right side. The pain finally became unbearable and he turned in". At that time he had a cough, which was non-productive. He admits that on one occasion, one month prior to admission to hospital, he coughed up considerable pus and all symptoms were relieved for a while.

February 2, 1931. Percussion note is clear and practically the same all over the chest. Auscultation reveals signs of a large cavity with harsh breath sounds. The area over which dulness on percussion was elicited at admission now gives almost cavernous breath sounds. The remainder of the chest is practically normal.

February 14, 1931. X-ray of chest (figure 4) shows almost complete resolution of the mass and is suggestive of a resolved pneumonia.

April 17, 1931. Guinea pig inoculated with pus from lung on January 27, 1931, is healthy and has gained in weight. Autopsy shows no signs of tuberculosis.

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Modern Conception of Retinal Detachment with its Relation to Internal Medicine*

By Clyde A. Clapp, M.D., *Baltimore, Maryland*

IT MAY seem to you that the question of detachment of the retina is rather a special subject to bring before a group of internists but in recent years there has been a new conception as to the etiology of one type of this condition, and a new line of therapy has been developed. This new conception of etiology and therapy as well as our frequent call upon the internists for help in diagnosis of the cause of these conditions warrants our consideration of this subject.

As you all know the retina is very loosely attached to the underlying tissue and can with comparative ease be separated from it. Detachments from the etiological standpoint are usually grouped under four heads:

(1) Those due to trauma;

(2) Those in which the retina is pulled away from its attachment by bands of connective tissue in the vitreous;

(3) Those in which the retina is pushed from its bed either because of a tumor or growth of the choroid or because of an extensive exudate;

(4) Those in which no particular cause can be determined, or the so-called idiopathic group.

Those cases which come under group 1, due to trauma, usually show marked improvement under rest and frequently entirely subside, leaving the retina fully attached and with normal fields of vision.

The cases in group 2, which are caused by contracting bands of fibrous tissue in the vitreous, usually follow a hemorrhage into the vitreous and the treatment is almost universally disappointing.

Group 3, consisting of those cases in which the retina is pushed from its bed, is of very great interest. Especially is this true in those cases resulting from massive exudate from the choroid, a condition which occurs in acute toxemia of pregnancy or in acute nephritis not associated with pregnancy.

I will show you two examples of the former, one showing a large detachment above and below and the other showing a complete peripheral detachment. The ophthalmoscopic picture is most striking and when first observed, the tendency is to give a very grave prognosis as to sight. One can, however, be very optimistic, since practically all of these detachments subside as the general condition improves.

*Presented at the clinical session of the Baltimore Meeting of the American College of Physicians, March 24, 1931, at the Wilmer Clinic.

and the retina becomes fully re-attached. The detachments in acute nephritis have a similar appearance to those of toxemia of pregnancy and both have a tendency to change their appearance very rapidly. My experience has been that when detachments occur as a result of nephritis not associated with pregnancy, the prognosis as to life is very grave and the patient usually dies within a few weeks or months.

Another very small number found in this group are due to a tuberculoma occurring in the choroid, which may elevate the retina. The use of the graduated tuberculin skin test as an assistance in diagnosis is to be recommended and tuberculin therapy is indicated. In a few cases beneficial results are obtained from this line of therapy, although often the pathological process is so advanced that improvement fails to take place.

Group 4, which is by far the most numerous, consists of those detachments which occur spontaneously and which were formerly known as idiopathic. It is to this group that I especially desire to call your attention in view of the new conception in regard to the etiology, and the new treatment instituted. The explanation given by Leber and later adopted by Gonin, that usually there is a localized disease of the retina, with atrophy and at times cystic formation which finally tears, leaving a gap or rent through which the vitreous penetrates, separating the retina from the choroid and giving the characteristic appearance, is the one widely held at the present time.

I have recently been fortunate in securing an eye which showed an old idiopathic detachment and I have had serial sections made in order to demonstrate, if possible, the presence or absence of such a rent. These sections show an old degenerated retina with marked cystic formation and at a short distance from the ora serrata there is a considerable rent in the retina through which the vitreous has penetrated thereby elevating the retina. This rent is comparatively small since ten sections upon either side shows a continuity of the retina. A similar rent also exists on the opposite side of the eye.

Gonin believed that the reason that results were not obtained in the treatment of these cases was that the opening in the retina allowed the vitreous to penetrate beneath the retina and this prevented its re-attachment. He therefore conceived the idea that if one could close these openings by searing their margins with the actual cautery, the retina would return to its bed. He first reported his results in 1919 and at the present time (July, 1930) claims that sixty per cent of these cases, if the detachment is recent, can be cured by this procedure. While American ophthalmic surgeons are not quite as optimistic as our European colleagues the procedure certainly offers more hope for restoration of vision than the old line of treatment of rest in bed for long periods, with hot packs and sweats.

How to Obtain More Autopsies*

By D. Schuyler Pulford, M.D., F.A.C.P., *Woodland, California*

THAT the percentage of autopsies obtained in any hospital or community is in direct proportion to the interest and efforts of the physicians in getting post mortems, is proven by numerous experiences. Some institutions and teaching hospitals have an average of eighty per cent, or more. In most city hospitals permits are exceedingly low, say from five per cent to twenty per cent.

Justifiable pride in ninety per cent autopsies obtained at the Woodland Clinic, for institutional deaths during 1930, and a belief that a discussion of the methods used in obtaining such a high percentage of necropsies will be of help to others, prompts the following report.

Reported Percentage of Permissions

The Council on Medical Education and Hospitals of the American Medical Association[1] in its report of the essentials in a hospital approved for interns revised to January 1, 1930, states that "inasmuch as the percentage of autopsies has come to be recognized as an index of the educational activities in a hospital, no institution will be approved for the training of interns which does not have a record of autopsies of at least fifteen per cent". This requirement has not been changed to date.

This Council reported in 1927[2] after a survey of 538 representative hospitals in the United States, the following percentages of autopsies:

3	hospitals with autopsies from	90 to	100%
2	hospitals with autopsies from	80 to	90%
9	hospitals with autopsies from	70 to	80%
13	hospitals with autopsies from	60 to	70%
8	hospitals with autopsies from	50 to	60%
26	hospitals with autopsies from	40 to	50%
42	hospitals with autopsies from	30 to	40%
91	hospitals with autopsies from	20 to	30%
35	hospitals with autopsies from	15 to	20%
107	hospitals with autopsies from	10 to	15%
122	hospitals with autopsies from	5 to	10%
80	hospitals with autopsies from	1 to	5%
None recorded		0 to	1%

Percentages have probably improved since that date but they are still lamentably low compared to those obtained in foreign countries.

Henry A. Christian[3] of Harvard Medical School states, "The number of necropsies obtained on patients dying in the hospital is perhaps the best single index of the professional efficiency of the hospital, of the amount of work devoted to the study of patients by members of the staff, of the eagerness of the staff to learn, and its teaching ability".

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Richards[4] in 1921, reported that in St. Luke's Hospital, New York City, one surgical service obtained forty-five per cent autopsies, and one ten per cent, and drew the conclusion that "success in obtaining necropsies depends upon the zeal and interest of the various staffs".

Doctor Bell,[5] in 1928, reported a high percentage of autopsies in teaching institutions in Minneapolis and stated that "the most important factor in increasing the number of post mortems is to get the physician deeply interested".

Doctor Kingsford,[6] in reviewing a year's autopsies in teaching institutions in Hanover, New Hampshire, reported forty-five autopsies upon sixty-eight deaths, 66.2 per cent. He attributed a rather rapid increase in the number obtained in his institution to the factor of "merely asking permission".

Robertson,[7] of Rochester, Minnesota, considers "percentage of permissions an index of the scientific spirit of any medical group". He also states that "when the clinical and laboratory staffs know that a serious effort will be made to get post mortem examinations and that they will be obtained in a large percentage of cases, the whole staff is stimulated to more careful work". And he feels that the patients will thereby be cared for more safely.

It seems probable that when hospital staffs become autopsy minded a minimum of 50 per cent autopsies should be obtained by all hospitals.

Autopsy Material

Sixty of the sixty-six patients who died at the Woodland Clinic twelve hours or more after admission in 1930 were autopsied. Although as institutional deaths are usually accorded only those patients who die after being in the hospital forty-eight hours or more, we felt that after twelve hours sufficient contact and interest in the clinical course was established to necessitate a post mortem examination to correlate clinical and pathological findings. If we include five cases dying less than twelve hours after admission who were not autopsied, we have seventy-one deaths with sixty autopsies, or 84.5 per cent. Obstetrical service baby deaths are not figured in this report because autopsies were not sought on this service, most of the deaths being due to prematurity. There were some autopsies done on these babies but neither the deaths nor the autopsies are included in these statistics.

Of those deaths occurring less than twelve hours after admission there were two from cerebral hemorrhage.

Table 1

	Admissions to Hospital	Per Cent	Deaths	Autopsies	Per Cent Autopsies
Medical	844	37	44	35	79.54
Surgical	1259	55	27	25	92.59
Obstetrical	157	8			
Total	2260	100	71	60	84.5
Patients dying less than 12 hours after admission			5		
Institutional Deaths			66	60	90.90

one from fractured pelvis, one from coronary occlusion and one from fractured skull and vertebra. Of the six real failures to obtain autopsies, one was a staff man dying of malignant hypertension; one, a terminal arteriosclerosis with hypertension; one, aplastic anemia; one, cancer of the rectum; one, subacute bacterial endocarditis, and one following a gall bladder operation.

A survey of the causes of death shows an overwhelming predominance of cardio-vascular deaths, sixteen of sixty, or 26.6 per cent, over one in four. Malignancy, pneumonia, peritonitis and accidents come in the order named with eleven, eight, eight and seven deaths. The other ten deaths include such rarities as Addison's disease, encephalitis, acute hepatitis and spider bite.

Besides these hospital autopsies the pathologist was called upon to perform eight coroner's autopsies for deaths occurring in or about Woodland and five other autopsies were done during the year in the city at the request of doctors who followed patients to death in homes or at the county hospital.

Methods of Obtaining Autopsies

For six years preceding 1930 autopsies at the Woodland Clinic averaged twenty-four per cent a year. Without any change in staff, hospital equipment or appreciable change in the number of patients, the figure rose the next year to ninety per cent. The staff members got together and said, "we need more autopsies". The results testify to the cooperation each man gave. Each doctor considered it his duty to obtain consent or see that someone did, and though not a pathologist, to perform a postmortem occasionally himself. The material obtained was later reviewed by the pathologist.

An outline of the routine arguments used in obtaining consent for an autopsy and the plan for interview of the relatives before and after post mortem was sent to each doctor on the staff. The complete cooperation of the two undertaking establishments in the city was obtained. This was accomplished in large part by permitting the embalming of the subject before the post mortem was done. Save in a few special cases where this seemed inadvisable from the standpoint of the pathologist, as for instance when cultures were wanted, embalming preceded the autopsy. Several autopsies were done at cities from twenty-five to fifty miles distant from Woodland, home town undertakers having removed bodies immediately after death. It was the rule that the first approach for permission was to be made by the doctor in closest touch with the patient. In case of failure the pathologist was called to present further explanation of the value of the necropsy to every one concerned. In our type of small clinic practice quite intimate relations are usually established between doctors and relatives, and much personal attention given so that on death the family often feels obliged to repay the doctor's kindness by permission for a post mortem. One or more of the following routine arguments was used in obtaining consent for autopsies: (1) The necessity of an autopsy in checking up on the exact cause of death. (2) The right of and benefit to the family to have this knowledge. (3) Benefit to the doctor and hospital. (4) Benefit to future patients, as treatment

is modified by increased knowledge gained by postmortems. (5) Aid in settling insurance claims. (6) That there is no delay and no extra charge. (7) That the high average per cent of autopsies permitted in the past by all classes of people in the best institutions testifies to the procedure being reasonable and proper.

No such interest in obtaining permissions could be kept alive without a strong stimulus and this was delivered in the form of a bimonthly or monthly clinical pathologic conference, fitting their frequency to the amount of material available, and not to any set date. Since it was the custom to have a weekly staff meeting for magazine reviews, reports of meetings or papers in preparation or heard or read elsewhere, it but remained for the pathologist to request the necessary time to present the material available and ready at any routine weekly staff meeting.

It seems best to have the pathologist as leader to present the case history of all deaths. The stimulus needed to induce and maintain interest in the clinicians depends in a large part on the excellence of the pathologist. The case history of the patient who had no autopsy often served to emphasize how important autopsies are, so they were also presented. After discussion by all doctors who saw the patient, gross specimens were shown and then microscopic slides projected. Closing discussion brings out any mistakes in diagnosis, delays or omissions in treatment and remarks as to similar cases seen formerly or elsewhere. Such universal favorable comment has been received from staff members as well as visiting physicians that it is planned to extend the clinical pathologic conference to include the material removed at the operating table together with the clinical reports of these surgical cases which present interesting tumors or situations.

Clinicians and pathologists alike admit their limitations and failures, for although death is, *per se*, admission of failure of the physician as treatment did not preserve life, yet often the pathologist, too, is at a loss to explain many causes of death, save by such unsatisfactory terms as surgical shock, toxemia, exhaustion, etc.

Those interested in developing logical and plausible points to convince relatives of the value of permitting a postmortem should read Emil Bogen's article printed in Hygeia, December, 1926. Also a very good detailed article on, "Answers to Layman's Objections to Postmortems", is that of Doctor Ralph Mills,[9] published in the Bulletin of the American College of Surgeons, of December, 1930. All pathologists and coroners should also familiarize themselves with Schultz's[10] recent article, "The Law of the Dead Human Body".

To summarize, it appears to the writer that the four most important factors in obtaining autopsies, in the order of their significance are: (1) obtaining one hundred per cent effort and interest on the part of the doctors concerned; (2) establishing a close personal understanding and trust and friendship between doctor and relatives during the patient's illness; (3) cooperation of the undertakers; (4) creating the proper public sentiment towards postmortems.

The Cost of Autopsies

The idea that necropsies cost too much money for small hospitals to consider is refuted by our experience. Much benefit is derived from a necropsy even if not done by the best pathologist and even if a complete microscopic and bacteriologic study is not made. When performed in a large pathology section of a university or teaching hospital the expense is great because of the complete detail and thoroughness of the work. The expense of an autopsy in Mt. Sinai Hospital in New York City in 1930, where four hundred and twenty-seven were done, was reported by Doctor Joseph Turner[11] to be ninety-two dollars each. Such a figure is not applicable to the smaller, less pretentious hospitals or clinic, nor is any such expense necessary. One should not imply from this statement that we advocate a poorer type of work. Until such expense can be met we would advise stimulating interest and increasing the percentage of necropsies until more money is available. This may in turn help to put in motion forces that will bring money for more detailed work. It might be helpful to call attention to the point where the expense of the Mt. Sinai system, for example, need not be shouldered by the smaller hospital or group of physicians.

At Mt. Sinai under the "Direct Charges" are listed:

(1) Pathologist's salary;
(2) Morgue space and overhead;
(3) Morgue keeper;
(4) Supplies;

and under "Indirect Charges":

(1) Time of staff interns and other attendant's expense in getting permission,
(2) Time consumed in the clinical preparation and presentation.

The greatest expense is probably the direct charge to the pathologist's salary. In order to reduce this a part-time pathologist may be employed, or a competent pathologist in the vicinity may be paid by the hospital or group of doctors interested for each post mortem done. All the other fixed charges having to deal with the morgue can be eliminated by the full cooperation of the undertaker. Autopsies can be performed as satisfactorily in an undertaking parlor as anywhere else, and gloves, instruments and supplies are often supplied by the undertakers in exchange for the doctor's good will. As to the indirect charge to staff and clinical pathological conferences, this is not to be thought of on a charge basis in a small hospital or city, for the educational element and the added prestige and ability developed by the doctor more than repays each man for his time. As far as the hospital and public are concerned the small expenditure necessary is well worth while, for as Doctor Turner says it is "eventually returned to the contributing public with compound interest in the form of improved practice of medicine in the hands of better trained physicians".

Summary

1. A practical inexpensive method of getting a high percentage of autopsies applicable to almost any community is outlined.

2. Not having a highly paid pathologist available is not a real obstacle.

3. Sixty of the sixty-six patients who died at the Woodland Clinic twelve hours or longer after admission

during 1930 were autopsied—90.91 per cent.

4. The time and expense incurred were more than justified by the increased knowledge of the physician and the consequent better handling of future patients.

5. A high percentage of autopsies can be obtained by merely stimulating enough interest in the doctors concerned to ask for them, and establishing a close bond between doctor and relatives during the patient's illness.

6. The cooperation of the undertakers can readily be obtained by courteous treatment and assistance in making embalming easy.

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Editorial

MOTTLED ENAMEL DUE TO FLUORIDE

In the condition known as mottled enamel the teeth are of normal form but present two different types of color change. They may have an opaque paper-white appearance but more frequently are irregularly mottled or stained yellow, brown or even black. The outer glazed enamel surface, Nasmyth's membrane, is present and appears to be normal, except in those cases which are termed 'corroded'. The brown stain can not occur unless the fundamental mottled defect of the enamel is present and may never develop. This alteration in the appearance of the enamel is highly disfiguring and once established cannot be remedied short of a difficult operative procedure. Moreover, practically every child born and reared in an area in which this condition is endemic is certain to have the condition to some degree. Thus the importance of this affection will readily be appreciated. The Pittsburgh Section of the International Association for Dental Research has recently devoted an entire program to a discussion of the nature, geographical distribution, and cause of mottled enamel.

The occurrence of mottled enamel at and near the town of Bauxite, Arkansas, has been studied by Kempf and McKay*. This community derived its water supply from wells about 255 feet deep. This deep-well water had a disagreeable alkaline taste, and many of the families continued the use of spring water for drinking. Evidence collected during the examination of school children showed that: (1) No cases of the enamel defect antedated the introduction of the deep-well water. (2) The oldest individual having this enamel defect was born about the time that the deep-well water was introduced. (3) All individuals who had used the deep-well water during any considerable period of enamel formation exhibited the defect. (4) No individual whose enamel had developed elsewhere exhibited the defect. (5) Certain individuals who were residents of this community and attended school there, but who actually lived beyond the distribution of the deep-well water and depended upon the original shallow wells, exhibited only normal enamel. Since the enamel of the temporary teeth almost never shows the defect and the calcification of the permanent teeth does not begin, on the average, until about one year after birth, it is evident that maternal nutrition is not even remotely related to the development of mottled enamel. The food supply of this group of people is from a central store, with the staple articles produced and manufactured

*KEMPF, GROVER A., and MCKAY, FREDERICK S.: Mottled enamel in a segregated population, Jr. Dental Research, 1932, xii, 121-140. (Reprinted from Public Health Reports, 1930, xlv, 2923.)

elsewhere. Locally grown products are used to some extent, but the diet of those exhibiting the enamel defect was similar in every respect, except as to source of water, to that of those who escaped.

In the town of Benton, about five miles distant from Bauxite, 124 children were examined. Of these, 103 were native to Benton and neighboring communities exclusive of Bauxite and these all showed normal enamel. The remaining 21 had formerly lived at Bauxite for longer or shorter periods. Of 16, who had lived in Bauxite for one year or more, 11 had mottled enamel.

On the strength of the evidence brought out by this study, together with reports of similar experiences elsewhere, it was decided to abandon immediately the deep-well water supply and to use water from the Saline River which was the source of supply of Benton. Oakley, Idaho, had previously abandoned its otherwise satisfactory water supply because of its apparent causal relationship to mottled enamel.

Ordinary methods of water analysis failed to identify the causal agent. While there were marked differences between the waters, these differences were not unlike those found in many other regions in which the native population remains entirely free from this enamel defect regardless of what the source of the water used might be. However, Churchill* reported the discovery of A. W. Petrey, using spectrographic methods, of fluoride in the deep-well water from Bauxite. He subsequently obtained samples of water from Colorado Springs; a well near Kidder, S.D.; a well near Lidgerwood, S.D.; and Oakley Idaho,—all localities in which the enamel defect was known to exist. The presence of fluorides was shown definitely in all cases. Quantitative estimation is difficult and is believed to give low values, but by the best method available the fluoride content of these waters was found to range from two parts per million for Colorado Springs to 13.7 parts per million for the deep-well at Bauxite, Ark. The survey was then broadened to include the water supplies for a number of cities, widely scattered, in which mottled enamel does not occur. Sixteen were found to have fluorides present, but in all cases to an amount less than one part per million.

The prevalence of mottled enamel in St. David, Arizona, was brought to the attention of investigators at the University of Arizona, in 1930, by A. E. Bard, a dentist of Tucson. Upon investigation* it was found that, with the exception of one family of three children living seven miles south of St. David and the sister-mothers of two other St. David families, every person born and reared in St. David, or coming there at an early age, showed mottling to varying degrees in every permanent tooth. Although

*Churchill, H. V.: The occurrence of fluoride in some waters of the United States, Jr. Dental Research, 1932, xii, 141-148. (Reprinted from Industrial and Engineering Chemistry, 1930, Anal. ed., ii, 263.)

*Smith, M. C.; Lantz, Edith, and Smith, H. V.: The cause of mottled enamel. Jr. Dental Research, 1932, xii, 149-159. Also: Technical Bull. No. 32, Agricultural Experiment Station, University of Arizona.

mottled enamel was absent from the teeth of domestic animals in St. David and had never been described from other endemic foci, the experimental production of mottled enamel in rats, guinea pigs and dogs was attempted. Diets in which calcium and phosphorus were present in deficient amounts, or in disproportion to each other, also those lacking in vitamin D, failed to produce abnormality entirely similar to the characteristic mottled enamel of man. Also, using both normal and abnormal diets, certain animals were given drinking water from St. David and a control series received distilled water. No destructive effect of the St. David water was noticed when the diet was adequate in all respects. When, however, the diet was deficient enough in itself to produce observable changes in the teeth, all the animals receiving the St. David drinking water gave evidence of this interference at an earlier age.

Realizing that the greater rate of growth of the incisors of rats as compared to children might influence the results of the experiment, further series of animals were given St. David water which had been concentrated to one-tenth of its original volume. In some instances the water residue was incorporated in the ration. Positive results were now obtained. Even though the diet was adequate in all respects, the enamel of rats receiving residue from St. David water quickly lost its translucency and normal yellow pigment, becoming whiter and more opaque than that of litter-mates receiving the same basal ration but with distilled water. In a month's time, the enamel of the affected animals was not only dull and chalky white in appearance, but also pitted and corroded. The condition produced seemed to be closely identical with the mottling of human teeth.

In another group of experiments, chemical compounds were added to the food or water, using such as for one reason or another had been suspected of interfering with enamel calcification. When sodium flouride in concentrations of 0.025, 0.05, and 0.1 per cent was added to the diet, the incisors of rats began to lose their luster within a week, and in a month a corroded, pitted condition of the enamel could be observed. In 1925, McCollum had noted the abnormal color in the teeth of rats when amounts of fluoride only slightly above those occurring in natural foods had been added to the diet. Wells in the neighborhood of St. David show a fluoride content of from four to seven parts per million. The well-water used by the family having the only children without the defect, that had been born and raised in the community, had a fluoride content of less than one part per million.

This work must be considered as advancing proof that mottled enamel is due to the fluoride content of the water supply of the afflicted communities. It adds another criterion to the list of those which must be taken into account in judging the suitability of a water supply. The "brown stain" of mottled enamel is evidently a secondary condition and as yet has not been satisfactorily explained.

Abstracts

Early Lesions of Rheumatic Endocarditis. By TIMOTHY LEARY, M.D. (Arch. Path., 1932, xiii, 1-22.)

The position of the author as medical examiner gave him opportunity to study the early phases of rheumatic endocarditis in persons who came to violent deaths while in apparent full health, or who died suddenly without hospitalization. Three patients, in the series utilized, provided the principal material. One was an apparently healthy boy of six years, whose death was due to violence, with an endocardial lesion of the mitral valve before verruca formation. An intermediate phase was found in a girl of 18 years, who had had mitral stenosis for eight years before her death, with an endocardial lesion of the tricuspid valve associated with verrucae formations in various stages. A late phase was obtained from a man, aged 51, who had an old, but not advanced, mitral process, with the lesion on the mitral valve, and showing pseudoverrucae due to thrombus formation. In the first case the contact edge of the valve was covered by a continuous layer of cells set on edge at right angles to the valve surface, giving the effect of an orderly palisade of cells guarding the injured valve surface. This must be interpreted as a reaction of defense against an injurious agent located on the surface. The cells of the palisade are believed to be evolved from fibroblasts. In the second case, the tricuspid valve showed a similar palisade arrangement between the verrucae and in the regions where no verrucae were found. In the third case pseudoverrucae made up of blood clot were found attached to areas of the mitral valve where there was a partially necrotic, dense and relatively acellular connective tissue. From this material it was possible to trace the evolution of the verrucae. Following injury to, and necrosis of, the cell palisade, the underlying fibroblastic tissue proliferates and groups of fibroblasts bulge upward at right angles to the surface underneath the hyaline necrotic masses. As the resulting verruca enlarges, histocytes appear among the fibroblasts. [The phases of this process are well illustrated by 23 figures.]

Streptococci Agglutination in Glomerulonephritis. By B. J. CLAWSON, and MACNIDER WETHERBY. (Proc. Soc. Exp. Biol. and Med., 1932, xxix, 566-567.)

The streptococcic agglutinating titers of the serums of 20 patients with glomerulonephritis were determined for a strain of streptococci recovered from the blood of a patient having acute rheumatic fever. All serums agglutinated in dilutions as high as 1:800. Five agglutinated at 1:800, ten at 1:1600, one at 1:3200, three at 1:6400 and one at 1:12800. The agglutinating titers of these serums were considerably higher than those found with the same strain with the serums of 110 normal individuals, of 50 patients with acute rheumatic fever, and of 300 patients with chronic arthritis. The relative height of the streptococcic agglutinating titers in glomerulonephritis suggested (1) an etiologic relationship and (2) a possible biologic method for differentiating renal insufficiency due to glomerulonephritis from renal insufficiency associated with primary hypertension.

Bacteriological Investigations on the Blood, Synovial Fluid and Subcutaneous Nodules in Rheumatoid (Chronic Infectious) Arthritis. By MARTIN H. DAWSON, M.D., MIRIAM OLMSTEAD, A.M., and RALPH H. BOOTS, M.D. (Arch. Int. Med., 1932, xlix, 173-180.)

In this study the term 'rheumatoid arthritis' is used to designate that form of chronic multiple arthritis more commonly called 'chronic infectious' or 'atrophic ar-

thritis. One hundred and five blood cultures, the majority in duplicate, were carried out on 80 patients suffering from rheumatoid arthritis, according to the technic of Cecil, Nicholls and Stainsby. As control material, 31 samples of blood from normal persons and 16 samples of sterile agar were subjected to similar manipulations. The blood cultures from patients suffering with rheumatoid arthritis failed to yield organisms that would be considered of etiologic significance. No significant difference was observed between the bacteria found in the blood cultures of patients and those observed during the culture of the control material. *Streptococcus viridans* was encountered occasionally during the culture of the control material as well as during the culture of specimens of the patients' blood. Twenty-three specimens of synovial fluid from patients with rheumatoid arthritis yielded no organisms of etiologic significance. Aerobic and anaerobic cultures of 12 subcutaneous nodules obtained from patients with rheumatoid arthritis likewise failed to yield organisms that could be considered of etiologic significance.

Elliptical Human Erythrocytes. By M. C. Terry, M.D., E. W. Hollingsworth, M.D. and Vicente Eugenio, B.A. (Arch. Path., 1932, xiii, 193-206.)

The authors have collected 50 instances of elliptical human erythrocytes, and have added two additional cases of their own. The autopsy findings in one case are given. Aside from a reddish purple color and semifluid consistency in the bone marrow of the femur, no changes which could be associated with the anomaly of the erythrocytes were found. When the blood of one of the patients was subjected to the action of hypotonic salt solution, the oval cells resembled normal erythrocytes in their behavior rather than the poikilocytes of a patient with anemia. The oval shape of the cells was shown to depend upon structure and not upon local environmental factors. The oval cells were found to be heavier than the round cells, and also more resistant than the round cells to the hemolytic action of hypotonic salt solution. An analysis of the entire group of cases establishes the condition as a hereditary anomaly which is not incompatible with health, which may occur in whites, blacks and mulattoes, and which is about equally divided in incidence between the sexes. It may be transmitted through either the male or female, and a generation may be skipped. All four blood groups are represented among the reported cases.

The Syndrome of Adrenal Hemorrhage in the New-Born. By Max A. Goldzieher, M.D., and Murray B. Gordon, M.D. Endocrinology, 1932, xvi, 165-181.)

Thirty-seven cases of adrenal hemorrhage in the new-born and 38 in older infants, all offering some clinical information, were gathered from the literature. To these, six personally observed instances, of which five were diagnosed during life, have been added. From a study of these 81 cases it was concluded that an *intra vitam* diagnosis of adrenal hemorrhage in the new-born may be made on the basis of a definite syndrome. This consists of two groups of symptoms: those due to acute adrenal insufficiency and those produced by internal hemorrhage. Either one of these may predominate. Acute insufficiency is made known by acute onset, high temperature, rapid respirations, petechial or purpuric rash, cyanosis and metabolic changes—especially hypoglycemia. Associated with these are gastro-intestinal and nervous disturbances. These may be accompanied or masked by signs of internal hemorrhage (shock, collapse, weak pulse) and local signs of abdominal distress, distention and the presence of a mass in one or both kidney regions. Suggested therapy consists of intravenous transfusion of blood, injection of glucose and the administration of a potent adrenal cortical extract.

Iodine Poisoning and Iodism from Lipiodol. By D. A. Carmichael, M.D. (Canadian Med. Assn. Jr., 1932, xxvi, 319-320.)

Two cases are described in which a combination of iodism and iodine poisoning followed the use of lipiodol. The first patient had received 20 c.c. of lipiodol by the transglottic method. Six hours later she became acutely ill with vomiting, diarrhea, faintness, pain in the hands, fingers, wrists, and face, followed almost immediately by urti-

carial wheals over the knuckles, wrists, forearms, forehead, nose, lips, chin, cheeks, ears, and sides of the neck. These became bullous vesicles, many of which were hemorrhagic. Tough crusts formed, beneath which the epithelium regenerated, and recovery without scar formation was complete at the end of three months. A second patient gave substantially the same symptoms and signs following the supraglottic introduction of 30 c.c. of lipiodol to confirm a diagnosis of bronchiectasis. The author believes that this combination of the irritant poison effects of iodine with the skin eruptions of iodism in these cases must indicate rapid absorption from the gastro-intestinal tract and that this is made possible by swallowing the sputum. He suggests that patients should be instructed that at no time during the procedure, or afterwards as long as the taste or smell of oil is recognized, should the sputum be swallowed. Careful search during the fluoroscopic examination will reveal any lipiodol in the stomach and if sufficient to contain even one grain of iodine, it should be removed either by gastric lavage, induced vomiting, or a brisk saline cathartic. Starch may be given as an antidote and continued as long as the vomited or aspirated material has a blue color.

A Pathologic Study of the Criteria Differentiating Chronic Gastric Ulcer, Cancer-on-Ulcer and Ulcerating Carcinoma of the Stomach. By W. H. BUEERMANN. (Northwest Medicine, 1932, xxxi, 49-54.)

From various sources the criteria to be applied in recognizing the development of gastric carcinoma upon gastric ulcer are assembled. In this manner the history of the evolution of this clinico-pathological conception is traced. The author finds that, at the present time, there is fairly general agreement that carcinoma does develop secondarily in a small percentage of chronic gastric ulcers. Definite pathologic criteria must be laid down and strictly adhered to in differentiating cancer-on-ulcer from ulcerating carcinoma. Clinically, the danger lies not so much in the possibility that cancer will develop upon a given gastric ulcer, as that an early ulcerating carcinoma may be masquerading as a benign calloused ulcer.

Reviews

It is with pleasure that attention is called to the fact that all of the books selected for review this month deal with the History of Medicine. This is a good sign. It is another indication of the growing interest in the cultural side of our work. It is in line with the increasing recognition given the subject of Medical History on the program of the San Francisco Meeting of the College, with the successful continuation in this country of such a journal as the *Annals of Medical History*, and with the increasing strength of both local and national societies for the prosecution of the study of this subject.

This is a period of notable anniversaries in Medical History. Less than two years ago was celebrated the tercentenary of the introduction of cinchona into medicine of the civilized world. This year, on October 24, another tercentennial should be noted, the birth of Antony van Leeuwenhoek. On March 24, the medical world did honor to the memory of Robert Koch, for fifty years before that day he announced the discovery of the tubercle bacillus.

It is well that so many local histories of medicine are being written. There should be one for every state and province. Material should be re-

corded while we still have with us those who saw the beginnings of so much that has proved of historical import in the growth of medical teaching and practice in North America.

History of Medicine in the United States. By FRANCIS R. PACKARD, M.D.; Editor, Annals of Medical History. 103 illustrations. Volume I, xxv + 656 pages; volume II, 666 pages. Paul B. Hoeber, Inc., New York City, 1931. Price, $12.00, for two volumes.

The production of a History of Medicine in the United States by the distinguished editor of the *Annals of Medical History* is an event of prime importance. To the more than 1300 pages of this great work the author has brought the experience and method of a trained historian who skillfully combines original source material with the exposition necessary to develop his theme. He is at his best in those sections to which this method is applicable. Since this was true of the greater part of the text, that statement alone constitutes enthusiastic praise. He succeeds admirably in writing interestingly and at the same time incorporating names and dates and facts. Only in those portions which deal with more recent events of somewhat local significance, in particular, the history of the individual medical schools, does interest lag and the method become encyclopedic. It should be obvious that if these topics are to be treated at all they must be thus sketchily covered. If the method of the historian seeking a full presentation from original sources had been applied to this portion, each short section would have become a monograph and no one human being could have accomplished the task. The author fully appreciated the limitations imposed for he states in the preface that if he had waited to gather complete data to a period even as remote as 1850, the task would not have been completed. The format and typography are excellent; the illustrations well chosen and well produced. A double index is provided, one of personal names and one of subjects; also a bibliography of twenty-four pages. This work should be in the possession of all interested in the History of Medicine. Seventy-five per cent of it can be read with interest by any practitioner and all of it is of great value for purpose of reference.

Imhotep to Harvey: Backgrounds of Medical History. By C. N. B. CAMAC, M.D., Assistant Professor of Clinical Medicine, College of Physicians and Surgeons, Columbia University, New York. Foreword by HENRY FAIRFIELD OSBORN, Sc.D., LL.D. xxv + 324 pages, 4 illustrations, five tables. Paul B. Hoeber, Inc., New York City, 1931, Price $3.75.

The author's seminars for fourth year medical students of The College of Physicians and Surgeons of New York are reflected in the pages of this book. In a series of chapters, each of which might serve as the basis for an informal exercise in Medical History, the background of the subject is developed. Preceding each the subject matter is briefly outlined, and in the last 20 pages, book lists are given, arranged to illustrate and complement the material of each chapter. Thus this book lends itself particularly to the library method of presentation. Illustrative material is found in a group of historical records and quotations from, or about, Servetus, Harvey, Copernicus, Galileo, Descartes, and Spinoza. We agree with the distinguished author of the foreword, that "The present volume will serve as an introduction to longer works, bringing the History of Medicine within the reach of medical undergraduates and those novices and initiates with whom the art of healing may become a delightful avocation, if not a vocation. To this large and rapidly increasing class of professional and nonprofessional readers we heartily recommend 'Imhotep to Harvey, Backgrounds of Medical History'."

History of Medicine in the Province of Quebec. By MAUDE E. ABBOTT, B.A., M.D., 97 pages, frontispiece and 41 illustrations. McGill University, Montreal, Canada, 1931. Price, $3.00.

This outline of the History of Medicine in the Province of Quebec was written for the publication known as *"The Storied Province of Quebec"*. It was originally divided into two parts, for the first of which,

covering the period from the discovery of Canada to 1800, the late Dr. Georges Ahern assumed responsibility. The second part, 1800 to the present time, was particularly assigned to Dr. Abbott. Through the death of Dr. Ahern it became necessary for Dr. Abbott to assume the responsibility of bringing this material together in a unified form. Dr. Abbott has succeeded in presenting a very interesting and informative account of the medical history of the province. While concerned with tracing the larger movements and the growth of significant institutions, Dr. Abbott has made free use of original sources with quotations, personal anecdotes, official records, and other citations which add greatly to the interest. The sections on Primitive Medicine, Scurvy among the First Settlers, the Rise of the Early French Hospitals, Michel Sarrazin, Inoculation and Vaccination, Great Epidemics of the Nineteenth Century, and Dr. James Barry are all of much more than local interest. Dr. Abbott has made a worthwhile contribution, not only to the Medical History of the Province of Quebec, but to that of the New World.

A Doctor of the 1870's and 80's. By William Allen Pusey, sometime President of the American Medical Association and of the American Dermatological Association. xiii + 153 pages. Illustrated. Charles C. Thomas, Springfield, Illinois. Price, $3.00 postpaid.

As a boy, the reviewer read and reread a simply written book entitled "The Country Doctor". Its authorship has long ago passed from memory, but its faithful reflection of the life and activities of a general practitioner in the prairie country rang true, and the skillful blending of comedy and pathos made an indelible impression. In Pusey's book we find again the record of the life and activities of the general practitioner in a rural community. This alone would justify its writing; but here the picture is drawn with skill and with tenderness. Between the lines one senses the anxiety of the son who fears that he will write too much of the virtues of his hero-father, and at the same time fears he is writing too little to measure up to what he knows to have been the just estimate of the man. This book should live on. It is not only a contribution to Medical History in the United States, but it is also a human document good to be read by the medical sons of medical fathers for more than one generation.

California Medicine (A Review). By John William Shuman, M.D., F.A.C.P. 182 pages. A. R. Elliott Publishing Company, 53 Park Place, New York City. Privately printed.

As previously stated it should be a source of great satisfaction to all interested in the history of Medicine in the United States that so many local histories have appeared in the last few years. This timely effort on the part of Dr. Shuman has made possible the preservation of the evidence of eye witnesses to many highly significant developments. In but a few years more such accounts will have become impossible. In California Medicine, the author records much that is of value, particularly to those whose special interest is in Los Angeles and its environs. To others medical, it will prove entertaining and informative, especially in regard to Indian and early Spanish Medicine and the doctors of the Gold Rush days. The author is to be congratulated on his easy narrative style. It is to be regretted that but a very limited edition is available.

Builders of American Medicine: Being a Collection of Original Papers Read before the Victor C. Vaughan Society of the University of Michigan Medical School. viii + 243 pages, 9 illustrations. George Wahr, Publisher, Ann Arbor, Michigan. 1932. Price, $2.00.

At the University of Michigan a self-perpetuating group of senior medical students is organized as The Victor C. Vaughan Society for the study of Medical History. The present volume contains twelve essays read before this group during the year 1930-31. The "Builders" who are the subjects of these essays are Zabdiel Boylston, Benjamin Rush, Ephraim McDowell, William Beaumont, Samuel D. Gross, Sr., Oliver Wendell Holmes, Austin

Flint, William Pepper, Silas Weir Mitchell, John Shaw Billings, Walter Reed and Victor C. Vaughan. Naturally, a senior medical student can seldom be a researcher in Medical History in the sense of bringing forth new knowledge from hitherto unknown or unappreciated original sources. Yet the vigor and freshness of the enthusiastic amateur stand out in these chapters, which must, of necessity, be largely fusions of tales that have been told before. This attractive little book deserves a wider distribution than that which it is likely to receive.

The History of Medicine: A Short Synopsis. By BERNARD DAWSON, M.D. (Lond.), F.R.C.S. (Eng.). xiv + 160 pages, 31 illustrations. The Macmillan Company, New York City, 1932. Price $2.50.

This small book contains a series of lectures delivered to junior medical students of Adelaide University. These lectures are intended to portray the continuity and increasing volume of the stream of medical knowledge rather than to present the details of the History of Medicine. The material is presented under seven chapter heads: Primitive Medicine, The Grecian Period, The Greco-Roman Period, the Dark Ages and the Hippocratic Tradition, The Middle Ages and the Universities, The Renaissance, and The Period of Consolidation. The style of this book is pleasing and the typography excellent. It can be recommended as fulfilling its stated purpose.

College News Notes

Acknowledgement is made of the receipt of gifts to the College Library of Publications by members, as follows:

Dr. Frank J. Altschul (Associate), Long Branch, N.J.—2 reprints;

Dr. Miles J. Breuer (Fellow), Lincoln, Nebr.—1 reprint;

Dr. Grafton T. Brown (Fellow), Washington, D.C.—1 reprint;

Lt. Col. Alexander T. Cooper (Fellow), Fort Myer, Va.—1 reprint;

Dr. Edward E. Cornwall (Fellow), Brooklyn, N.Y.—1 reprint;

Dr. John J. Dumphy (Associate), Worcester, Mass.—2 reprints;

Dr. Hyman I. Goldstein (Associate), Camden, N.J.—3 reprints;

Dr. John R. Hamel (Fellow), Portland, Maine—2 reprints;

Dr. Ronald L. Hamilton (Fellow), Sayre, Pa.—1 reprint;

Dr. Robert A. Knox (Fellow), Washington, Pa.—1 reprint;

Dr. George B. Lake (Associate), Highland Park, Ill.—3 reprints;

Dr. David E. Markson (Fellow), Chicago, Ill.—1 reprint;

Dr. Oliver T. Osborne (Fellow), New Haven, Conn.—1 reprint;

Dr. Virgil G. Presson (Associate), Tucson, Ariz.—1 reprint;

Dr. Karl Rothschild (Associate), New Brunswick, N.J.—2 reprints;

Dr. Virgil E. Simpson (Fellow), Louisville, Ky.—3 reprints.

Dr. Carl V. Vischer (Fellow), Philadelphia, Pa.—1 reprint.

Dr. Guy G. Lunsford (Fellow), Commissioner of Health, Millen, Georgia, addressed the annual meeting of the Georgia Public Health Association, January 22, 1932, on "Typhoid and Sanitation."

Dr. Arthur C. Morgan (Fellow), Philadelphia, Pa., was recently appointed by Governor Pinchot of Pennsylvania as a member of the State Board of Medical Education and Licensure.

Capt. Kent C. Melhorn, M.C., U.S.N. (Fellow), Washington, D.C., was detached lately from the Bureau of Medicine and Surgery, Navy Department, and reported to the State Department for duty as physician to the American Delegation to the General Disarmament Conference, Geneva, Switzerland. Captain Melhorn was appointed to

the Medical Corps of the Navy in 1907. Since September, 1930, Captain Melhorn has been in charge of the Division of Personnel, Bureau of Medicine and Surgery.

Dr. Hyman I. Goldstein (Associate), Camden, N. J., is the author of an article in the *Medical Times* (N.Y.) for January, 1932, entitled "Mitral Stenosis." He is also the author of an article in the *Journal of the Medical Society of New Jersey* for February, 1932, entitled "Erythema Nodosum and Erythema Multiforme," and of one in *International Clinics* (Phila.) for March, 1932, entitled "Recent Advances in Treatment."

Dr. E. J. G. Beardsley (Fellow), Philadelphia, Pa., Governor for Eastern Pennsylvania, was the guest speaker at the Cambria County Medical Society at Johnstown, Pa., on February 11, 1932. His subject was "The Science and the Art of Medicine."

Dr. David E. Markson (Fellow), Chicago, Ill., read a paper entitled "Newer Concepts on Etiology and Treatment of Arthritis" before the DuPage County Medical Society on January 16, 1932. On January 28, he presented the "Report of a Case of Diabetic Coma, with Blood Sugar of 900 mg., with Recovery" before the staff of the Norwegian American Hospital, and on March 3, addressed the North Side Branch of the Chicago Medical Society on "Therapeutic Fever in the Treatment of Arthritis."

Dr. John L. Garvey (Fellow), Milwaukee, Wis., recently presented a paper on "Calcified Angiomas of the Brain," together with a report of a case, before a meeting of the Chicago Neurological Society.

At a Symposium on Arthritis given by the Section of Internal Medicine of the Los Angeles County Medical Association on February 3, 1932, the following Fellows of the College contributed to the program:

"Arthritis Due to a Definite Organism"
Dr. Roland S. Cummings, Los Angeles; Discussion opened by Dr. Roy Thomas, Los Angeles.

"Arthritis Due to Metabolic Disturbances"
Dr. S. M. Alter, Los Angeles; Discussion opened by Dr. Paul B. Roen, Hollywood.

"Arthritis Deformans"
Dr. John V. Barrow, Los Angeles.

Dr. John W. Shuman, Los Angeles, is President of the organization and Dr. John V. Barrow, Los Angeles, is Secretary. Dr. S. M. Alter was Chairman for the Symposium.

Dr. Edward J. Engberg (Fellow), St. Paul, Minn., read a paper on "The Present Extent and Value of Annual Registration" before the Federation of State Medical Boards of the United States held in Chicago on February 15 and 16, 1932, in connection with the Annual Congress on Medical Education, Medical Licensure, and Hospitals.

Dr. Paul J. Connor (Fellow), Denver, Colo., was elected President of Staff of the Presbyterian Hospital of Colorado at a meeting of the Staff in January.

Dr. Erwin D. Funk (Fellow), Wyomissing, Pa., is in Germany pursuing further studies in Pathology.

An interesting Annual Report of the St. Edwards Mercy Hospital of Ft. Smith, Ark., was recently received. Dr. S. J. Wolferman (Fellow) is Chief of Staff. Dr. Arless A. Blair (Fellow) is Vice President of the Clinical Staff as well as being a member of the Executive Staff.

Dr. Edward V. Goltz (Fellow), St. Paul, Minn., was elected President of the Ramsey County Medical Society at the November meeting.

Dr. Lorenz W. Frank (Fellow), Denver, Colo., was elected President of the Medical Society of the City and County of Denver at the annual meeting on January 4, 1932.

Dr. Edward W. Jackson (Fellow), formerly of Rochester, N. Y., has recently become associated with the Pontoin-Brown

Clinic Hospital of Edinburg, Texas, as Chief of the Medical Staff.

Dr. William Engelbach (Fellow), New York City, addressed the American-Hungarian Medical Association at the New York Academy of Medicine on February 15, 1932, his subject being "The Growth Hormone." Dr. Englebach also delivered an address on "The Anterior Pituitary Lobe" before the Bedford Medical Society, February 25, 1932.

Upon examination of the March 1 issue of *Progress Notes* published by the Atlantic City Hospital, Atlantic City, N. J., we note that the following Fellows and Associates of the College are on the General Staff for 1932: Dr. Samuel Barbash (Fellow); Dr. D. Ward Scanlan (Fellow); Dr. Samuel L. Salasin (Fellow); Dr. Clarence L. Andrews (Fellow); Dr. Sidney Rosenblatt (Associate); Dr. Harold S. Davidson (Fellow); Dr. Philip Marvel, Jr. (Fellow); and Dr. Hilton S. Read (Associate). Dr. Philip Marvel, Sr., (Fellow) and Dr. W. Blair Stewart (Fellow), Governor for New Jersey, are Honorary Members of the Staff.

Dr. Frederic J. Farnell (Fellow), Providence, R. I., Chairman of the Public Welfare Commission, State of Rhode Island, is the author of a signed article appearing in *The United States Daily*, Washington, D.C., February 17, 1932, entitled "Plan for Public Welfare Work in Rhode Island."

The following Fellows of the College are members of the Committee on Nominations of the National Tuberculosis Association: Dr. Stuart Pritchard, Battle Creek, Mich., Chairman; Dr. Frederick T. Lord, Boston, Mass.; Dr. Munford Smith, Los Angeles, Calif. At the Twenty-eighth Annual Meeting of the National Tuberculosis Association, to be held at the Anters Hotel, Colorado Springs, Colorado, June 6-9, 1932, Dr. Pritchard will give the Report of the Committee on Nominations.

At this meeting, according to the Preliminary Program, the following Fellows will present papers: Dr. Gerald B. Webb, Colorado Springs; Dr. Clarence L. Hyde, Akron, Ohio; Dr. John W. Flinn, Prescott, Ariz.; Dr. E. K. Geer, St. Paul, Minn.; Dr. H. A. Burns, Ah-gwah-ching, Minn., and Dr. Carl H. Greene, Rochester, Minn.

Dr. I. D. Bronfin (Fellow), Denver, Colo., will speak at the Spring Meeting of the American Sanatorium Association, June 6 and 7, 1932, to be held at the Brown Palace Hotel, Denver, Colo., and F. E. Harrington (Fellow), Minneapolis, Minn., and Dr. Benjamin W. Black (Fellow), Oakland, Calif., will appear on the program of the American Public Health Association, whose Western Branch Meeting will be held June 9-11, 1932, in Denver.

Dr. Ada E. Schweitzer (Fellow), Indianapolis, Indiana, Child Hygiene Director for the Indiana State Board of Health, Division of Infant and Child Hygiene, is responsible, in conjunction with Dr. Wm. F. King, State Board of Health Commissioner for Indiana, for the novel idea of designating May Day as Child Health Day in that State. Pamphlets have been broadcast to homes, churches, and institutions of various kinds throughout the state, suggesting programs of activity and instruction along health lines for use in observing this special health day. Individuals and groups putting these or other plans into practice are urged to report the same to Dr. Schweitzer in order that the movement may incorporate permanently the advances made this year.

Dr. V. C. Rowland (Fellow), Cleveland, Ohio, was the guest of Dr. A. B. Brower (Fellow), Dayton, Ohio, Governor for Ohio, at a dinner at the Van Cleve Hotel on March 4, 1932. Later the same evening he addressed the Montgomery County Medical Society on "Differential Diagnosis of Chronic Colitis." En route to Dayton, Dr. Rowland had spoken before the Fayette County Medical Society at Washington C. H., Ohio, in connection with their campaign on Diphtheria Immunization, his subject being "Periodic Health Examinations." At this meeting he represented the Periodic Health Examination Committee of the Ohio State Medical Association.

Dr. Alfred Friedlander (Fellow), Cincinnati, Ohio, delivered an address before the Medical Forum of Pittsburgh on the evening of February 13, embodying the results of studies on the "Reticulocyte Count in Normal and Abnormal Conditions."

Dr. Albert W. Ferris (Fellow), East Orange, N.J., has resigned his position as Senior Physician on the Staff of the Glen Springs Health Resort, Watkins Glen, N. Y., because of illness. Dr. Ferris spent nearly fifteen years in this service, besides having been formerly President of the N. Y. State Commission in Lunacy (now the Department of Mental Hygiene), Medical Editor for many years of the *New International Encyclopedia and Year Book*, and the author of over forty articles on medical topics, in various medical publications. He has now retired from practice and is living at 111 N. Walnut Street, East Orange, N.J.

Dr. Walter M. Simpson (Fellow), Dayton, Ohio, was a guest of the Medical Service of the Fifth Avenue Hospital, New York City, on February 19, 1932, presenting a paper on "Tularemia" on that evening.

Dr. Charles J. Bloom (Fellow), New Orleans, held a clinic on March 3 in the city of McComb, Mississippi, and the same evening gave a paper entitled "Common Respiratory Infections in Infants and Children."

Dr. Joseph H. Barach (Fellow), Pittsburgh, addressed The Mohoning County Medical Society at Youngstown, Ohio, on February 16, 1932. Dr. Barach spoke on the topic, "The Etiology, Classification, and Treatment of High Arterial Pressure."

Dr. Anthony Bassler (Fellow), New York City, lectured to the senior students of Jefferson Medical College and to the senior and junior students of Hahnemann Medical College of Philadelphia on March 23, 1932, speaking on the Physiology of the Pancreas, with special regard to his test for judging the efficiency of the external secretion of the pancreas and its clinical application.

On February 24, 1932, Dr. J. Reid Broderick (Fellow), Savannah, Georgia, addressed the First District Meeting of the Georgia Medical Society in Statesboro, Georgia, on the subject, "Bronchial Asthma."

OBITUARIES

DOCTOR HUGH SPAULDING WILLSON

Doctor Hugh Spaulding Willson (Fellow), died from acute coronary thrombosis at his home in La Jolla, California, on the 12th of December.

Dr. Willson was born in 1877 at Plain View, Minnesota. He was graduated in medicine by the University of Minnesota in 1904. After practicing as assistant city physician in Minneapolis for eighteen months he went to Crystal, North Dakota, where he practiced until 1912. Following a year's service with the Mayo Clinic at Rochester, Minnesota, Doctor Willson went to Minneapolis where he built up a gastro-intestinal clinic in which he, and the physicians he had associated with him, conducted a large and widely known practice. At the outbreak of the war, Doctor Willson went into Military service as a consulting physician. After nine months at Camp Kearney he went overseas with Base Hospital No. 70. After the war Doctor Willson reopened the Clinic in Minneapolis. He remained there until 1926, when, forced by ill-health, he went to La Jolla, California, where his wife, Mary Richmond, to whom he was married in 1907, now survives him. Doctor Willson found the rest and change to

California so beneficial that he opened offices in La Jolla. The return to activities in his profession gave him much comfort and brought him high esteem among his many friends and patients who deeply regret his untimely death.

(Furnished by EGERTON CRISPIN, M.D., F.A.C.P., Governor for Southern California).

DOCTOR HOWARD H. BELL

Dr. Howard H. Bell (Fellow), St. Louis, Missouri, died January 7, 1932, age forty-seven years.

Dr. Bell was born at Lewistown, Pennsylvania, attended High School there, and later entered the Philadelphia College of Pharmacy, from which he graduated as a Pharmaceutical Chemist in 1907. In 1909 he was awarded the degree of Doctor of Pharmacy from the same institution. He entered the University of Pennsylvania School of Medicine, and graduated with the degree of Doctor of Medicine in 1912. He was Instructor in Pathology and Bacteriology at the University of Alabama, 1913 to 1919; Assistant Instructor and Associate in the Department of Pathology, and later Associate Professor of Bacteriology at the Washington University School of Medicine, St. Louis, these appointments extending from 1914 to 1924. During 1924 and the first half of 1925, he was connected with the Department of Medicine of the University of Cincinnati, and in 1925 went to the St. Louis University School of Medicine as Assistant in Medicine, which appointment he held at the time of his death. He was also Tuberculosis Controller for the city of St. Louis.

Dr. Bell was the author of many publications appearing in the leading journals of the country. During the World War he served at Rouen, Dijon, Langres, and in the Balkans. In all he served twenty-eight months in foreign service successively as First Lieutenant, Captain and Major. He was cited by the Officers Municipaux de Langres and was decorated by the King of Rumania.

He was a member of the St. Louis Medical Society, an Ex-President of the Trudeau Club, a member of the Missouri State Medical Society, a Fellow of the American Medical Association, as well as being a member of many other scientific organizations. He was elected a Fellow of the American College of Physicians on April 8, 1929.

DOCTOR MALLIE ADKIN CLARK

Dr. Mallie Adkin Clark (Fellow), Macon, Georgia, died February 6, 1932.

Dr. Clark was born in Russell County, Alabama, September 1, 1866. His preliminary education was obtained under his father's direction, and in 1885, he received his A.B. degree from Mercer University, and in 1911, his LL.D. degree from the same institution. He received his M.D. degree from Bellevue Hospital Medical College in 1890. For several years thereafter, he practiced medicine in Bluffton and Barnesville, Georgia, going to Macon in 1897, where he remained in active practice until the time of his death. From 1898, he was on the Faculty of Mercer University as teacher of Medical Jurisprudence in the Law School, and Materia Medica in the School of Pharmacy. For sev-

eral years, he was a member of the Board of Trustees of this university.

Dr. Clark had been an active member of the local medical society in Macon for many years, and was past President of the Medical Association of Georgia, and at the time of his death was its Parliamentarian. He was a Fellow of the American Medical Association, and was elected a Fellow of the American College of Physicians on January 1, 1921.

Dr. Clark was a member of the staff of the Macon Hospital for many years, and had been a member and chairman of the Governing Board of that hospital.

He was pre-eminently a student, setting aside a part of every day for real study. His knowledge of medical sciences was well nigh encyclopedic. Those who sought of him information often said he seemed not to forget anything he had read. He gave willingly of his time and talents to those who sought his assistance; his opinion was respected. With him, his profession was his life; his recreation consisted of study of science and literature. He was devoted to his patients and felt keenly their sorrows and rejoiced in their joys.

(Furnished by JAMES A. FOUNTAIN, M.D., F.A.C.P., President, Medical Society of Bibb County).

The Importance of Finger-Borne Infection

"IN THE transfer of this type of infection [diphtheria] from one person to another, the fingers are probably the chief agents. It has been said, 'Who can doubt that if the salivary glands secreted indigo, the fingers would continuously be stained a deep blue, and who can doubt that if the nasal and mouth secretions contain the germs of disease these germs will be almost as constantly found upon the fingers? All successful commerce is reciprocal and in this universal trade of human saliva the fingers not only bring foreign secretions to the mouth of their owner, but there, exchanging them for his own, distribute the latter to everything that the hand touches. This happens not once, but scores and hundreds of times during the day's round of the individual. Everyone is busily engaged in this distribution of saliva, so that the end of each day finds this secretion freely distributed on the doors, window sills, furniture, and playthings in the home, the straps of trolley cars, the rails and counters and desks of shops and public buildings, and, indeed, upon everything that the hands of man touch. What avails it if the germs do die quickly? A fresh supply is furnished each day.'

"Bearing in mind the aforementioned fundamental principles, the following

measures are recommended for the prevention of diphtheria, in the application of which every parent, schoolteacher, and family physician should render active cooperation: (1) Strict adherence to the rules of personal hygiene, and (2) the immunization of all people who are likely to have diphtheria as shown by the Schick test."

(From *Health News*, United States Public Health Service, March 16, 1932.)

SCIENTIFIC ARTICLES IN FORTHCOMING NUMBERS OF THE ANNALS OF INTERNAL MEDICINE

The May Number

Rheumatic Heart Disease. A Review. ..... Clough Turrill Burnett

Early Manifestations of Rheumatic Infections in Young Children. C. C. McLean

Causes, Classification and Differential Diagnosis of Anemias. Based on the Detailed Examination of over 200 Patients and a Study of the Literature. ..... Edwin E. Osgood and Howard D. Haskins

A Comparative Study of the Use of Whole Liver, Liver Extract and Ventriculin ..... Hugo A. Freund and Alvin E. Price

Raynaud's Disease Affecting Men .... Edgar V. Allen and George E. Brown

Does Liver Therapy Benefit the Diabetic? ..... Elmer L. Sevringhaus

Primary Sclerosis of the Pulmonary Artery. Report of a Case ..... Edgar R. Pund and Thomas B. Phinizy

Gonorrheal Endocarditis. Summary of the Literature and Report of a Case ..... Arthur M. Hoffman and Floyd C. Taggart

The Significance of Lymphatic Tissue and Adenoma-like Areas in the Thyroid Gland ..... L. R. Himmelberger

Pulmonary Lesions in Human Tularemia. Pathologic Review and Report of a Fatal Case ..... Staige D. Blackford

Oliver Goldsmith, M.D. ..... Louis H. Roddis

The June Number

An Experimental Basis for Intravenous Vaccine Therapy in Chronic Arthritis with a Summary of Results Obtained in Patients ..... B. J. Clawson and M. Wetherby

Hypertension and Diabetes ..... Henry J. John

The Fallacy of the Weighed Diet in the Treatment of Diabetes Mellitus ..... Helmuth Ulrich

Myxedema. A Case Report ..... Henry B. Gotten

Hypothyroidism without Myxedema. John B. Youmans and Samuel S. Riven

Ventricular Paroxysmal Tachycardia, with Report of a Case ..... Edward W. Hollingsworth

Control of the Tick Borne Diseases, Methods and Economics .. Noxon Toomey

The Local and Constitutional Pathology of Bronchial Asthma ..... Ian C. Macdonald

The Etiology of Colds ..... John E. Walker

A Layman Considers Migraine ..... Walter B. Sheppard